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This report reviews the potential environmental hazard from the commercial use of acrylamide and its derivatives. For the most part, acrylamides are used in the production of polyacrylamides, which are used as flocculants in sewage and wastewater treatment (~ 40%) and as a strengthener in the pulp and paper industry (~ 20%). Water leaching of the monomer from the polymer has been demonstrated by effluent monitoring, but the monomer has been demonstrated to be biodegradable. Acrylamide causes peripheral neuropathic effects and is, therefore, of occupational concern. Its other toxicological properties are not well defined. From the available information, acrylamides do not appear to be widespread contaminants but local incidences of contamination may occur.

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ENVIRONMENTAL CONTAMINANTS:
ACRYLAMIDES

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Executive Summary

Of the acrylamide compounds reviewed, only acrylamide is produced in sizable quantities; the 1973 estimate is 40 million pounds. For the most part, acrylamides are consumed in the synthesis of commercial polyacrylamides. The major uses of polyacrylamide are for waste water flocculants (40% of production) and in the pulp and paper industry (20% of production); there are a number of minor uses of polyacrylamides, such as adhesives and flooding agents for petroleum recovery. Acrylamide monomer is marketed as a chemical grout and soil stabilizer for use in dams, foundations, and tunnels (quantity used is less than 5% of the total production).

The major source of acrylamide environmental contamination appears to be from the release of residual acrylamide monomer from the polymers. British effluent monitoring data support this contention, although even the highest levels do not exceed 50 ppb. Contamination of media other than water does not seem likely. Acrylamide is very water soluble and biodegradable, and therefore, does not bioconcentrate.

From the current pattern of use and release, it does not appear that widespread environmental contamination with acrylamide is likely; however, there is some concern that local incidents of significant acrylamide contamination could occur in aqueous systems including drinking water. A more definitive study of the uses of polyacrylamide is needed to determine the likelihood of such occurrences.

In considering its biological aspects, three possible adverse effects from acrylamide are apparent: neurotoxicity, carcinogenicity, and toxicity to aquatic organisms.

Acrylamide is a neurotoxin and, as such, is a proven occupational hazard. Certain acrylamide analogs are also neurotoxic and should be considered as potential occupational hazards. However, repeated dosing studies with various laboratory mammals indicate that there is a threshold concentration below which the neurotoxic effects of acrylamide are not induced. Therefore, the neurotoxicity hazard would seem to be of environmental concern primarily when incidents of excessive acrylamide concentrations might occur in drinking water.

The lack of information on carcinogenicity is a major impediment to a more definite evaluation of acrylamide environmental hazard. While acrylamide has not been specifically tested for carcinogenicity, it is able to bind and possibly alkylate RNA and DNA and does alkylate protein, all three of which are associated with chemical carcinogens. Therefore, carcinogenicity testing of the commercially important acrylamides appears desirable.

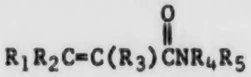
The current limited information on fish toxicity indicates that ambient levels as found in the British monitoring study should not affect these aquatic organisms. Because acrylamide seems to biodegrade rapidly, the lack of toxicity data on many aquatic organisms does not seem crucial. Again, however, the available data are not sufficient to fully assess the possible effects on aquatic biota where incidental excessive concentrations of acrylamide might occur.

I. Physical and Chemical Data

A. Structure and Properties

1. Chemical Structure

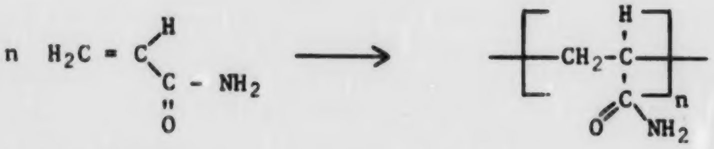
Acrylamide and its chemically related commercial products are α,β unsaturated amides with the following structure:



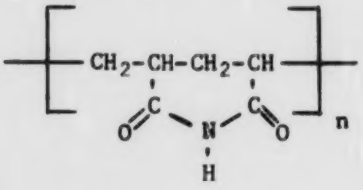
$$R_1R_2C{=}C(R_3)\overset{\overset{O}{\|}}{C}NR_4R_5$$

Of the several hundred acrylamide derivatives that have been prepared (MacWilliams, 1973), only the nine compounds listed in Table 1 (p. 3) appear to be produced in commercial quantities (SRI, 1975). The parent compound, acrylamide (R_1, R_2, R_3, R_4, and R_5 = H), is, by far, the most significant commercial product, and the quantity produced is almost totally consumed in the synthesis of polymers. The other commercial products consist of one carbon-substituted derivative, methacrylamide ($R_3 = CH_3$), and seven N-substituted compounds.

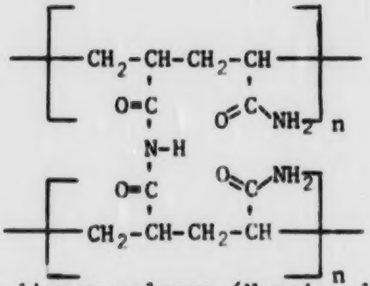
Polyacrylamide is a nonionic linear polymer prepared by free radical addition polymerization (Thomas, 1964):



Either linear or cross-linked polymers may be prepared from acrylamide and its derivatives, with molecular weights on the order of 10^3 - 10^7, depending on reaction conditions. Cross-linking via intra- or intermolecular imidization produces structures such as

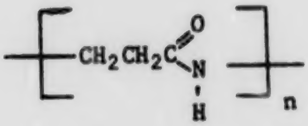


and



and reduces the high water solubility of the linear polymer (Norris, 1967b).

Polyamide formation (rather than polyacrylamide) is favored by heating acrylamide with a strong base and gives poly-β-alanine (nylon 3) (Thomas, 1964):



Copolymerization with other vinyl polymers occurs readily and is a means of producing polymers with a wide range of properties.

2. Physical Properties of Pure Material

Acrylamide is a white, crystalline solid noted for its high solubility in water and other polar solvents; most other vinyl monomers are liquids or gases with low water solubilities (Thomas, 1964). Table 1 summarizes the physical properties of acrylamide and selected derivatives. Table 2 summarizes the solubilities of these compounds in common solvents. Figure 1 shows the UV spectrum of acrylamide, and Figure 2, the vapor pressure of the solid and molten liquid.

The physical properties of polyacrylamides vary widely, depending on the method of manufacture, the inclusion of copolymers, etc. Linear polyacrylamide is a white, odorless solid, soluble in water, and insoluble in methanol, ethanol, acetone, and hexane. It is compatible with most natural and synthetic water-soluble gums, dispersants, and surfactants (Swift, 1957). In very dilute solutions, polyacrylamides of high molecular weight are efficient flocculants which cause rapid agglomeration and sedimentation of finely divided solids in suspension (Norris, 1967b). Solutions of polyacrylamides at least as high as 1% can be made in formamide, lactic acid, acrylic acid, and molten urea. At 85°C or less, the maximum possible concentration of polyacrylamide is less than

Table 1. Physical Properties of Acrylamide and Related Compounds (MacWilliams, 1973; Bikales and Kolodny, 1963; Bikales, 1970; Riga, 1975; Anon., 1975 a, 1976 a; Lubrizol., 1974)

Compound	Structure	MW	MP °C	BP °C (mmHg)	Vapor Pressure Liquid mmHg (°C)	Vapor Pressure Solid mmHg (°C)	Density g/cm³	Refractive Index n_x	Refractive Index n_y	Refractive Index n_z
Acrylamide	$CH_2=CHCONH_2$	71.08	84.5 ± 0.3	87(2) 103(5) 125(25)	2(87) 5(103) 10(116.5) 25(125)	0.007(25) 0.033(40) 0.07 (50) 0.14 (40) 0.21 (50)	1.122	1.460	1.550	1.581
Methacrylamide	$CH_2=C(CH_3)CONH_2$	85.11	110				1.10			
N-Methylolacrylamide	$CH_2=CHCONHCH_2OH$	101.10	78.5-79.0		Commercial form is 60% aqueous solution					
N,N'-Methylenebis-acrylamide	$(CH_2=CHCONH)_2CH_2$	154.17	185 (decomp.)				1.235	1.515	1.595	1.611
N-Isopropylacrylamide	$CH_2=CHCONHCH(CH_3)_2$	113.16	64-65		2(89-92)					
N-*t*-Octylacrylamide	$CH_2=CHCONHC(CH_3)_2C_5H_{11}$	183.29	83							
N-*t*-Butylacrylamide	$CH_2=CHCONHC(CH_3)_3$	127.18	128-130				1.015	1.465	1.495	1.575
2-Acrylamido-2-methyl-propanesulfonic acid	$CH_2=CHCONHC(CH_3)_2CH_2SO_3H$	207	185 (decomp.)							
N-Isobutoxymethyl-acrylamide	$CH_2=CHCONHCH_2OCH_2CH(CH_3)_2$	157		99-100(.03)			0.98			

Table 2. Solubilities of Acrylamides and Selected Derivatives[a] (MacWilliams, 1973)

		Acrylamide	N-Methylolacrylamide	N,N'-Methylene-bisacrylamide	2-Acrylamido-2-methyl-propanesulfonic acid[b]	Methacrylamide	N-Isopropyl-acrylamide	N-Isobutoxy-methyl-acrylamide[d]
Water	25°C		soluble	3	150	∞		insoluble
	30°C	215.5					21	
	50°C			6.5			17	
Methanol		155	150	8.2	8.7 (30°C)	soluble	∞	soluble
Ethanol		86.2	160	5.4	10 (78°C)	soluble	∞	
Acetonitrile		39.6			insoluble			soluble
Dioxane		30	soluble - hot	1.1	insoluble		∞	
Acetone		63.1	partially soluble	1.0		soluble	∞	soluble
Tetrahydrofuran					insoluble			soluble
Chloroform		2.66		0.3	insoluble		∞	soluble
Benzene		0.346	insoluble	<0.1	very insoluble	soluble	∞	soluble
Ethyl acetate		12.6	partially soluble	0.4	insoluble	soluble	∞	soluble
Methylmethacrylate					very insoluble		∞	
n-Heptane		0.0066	insoluble	<0.02			slightly soluble	insoluble
1,2-Dichloroethane[c]		1.50						
Dimethylformamide[c]		119						soluble
Dimethyl sulfoxide[c]		124						
Pyridine[c]		61.9						
Carbon tetrachloride[c]		0.038						soluble

[a] g/100 ml @ 30°C

[b] Lubrizol Corp. (1974)

[c] Anon. (1969)

[d] Anon. (1976 a)

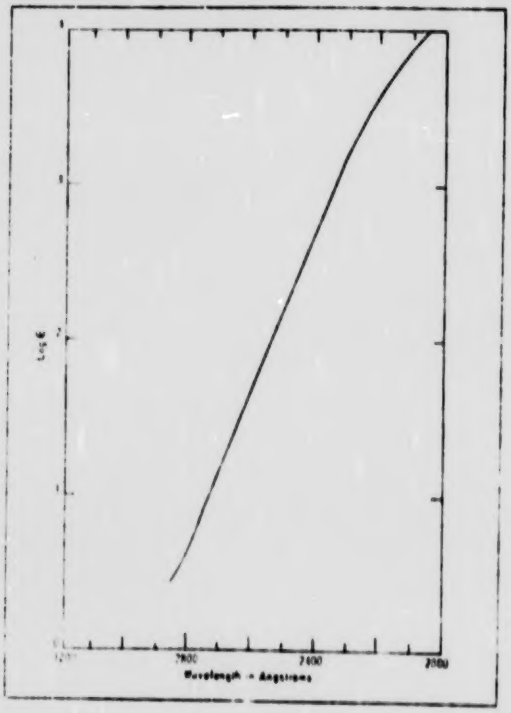


Figure 1. Ultraviolet Absorption Spectrum of Acrylamide in Water (Anon., 1969) (Reprinted with permission from American Cyanamid Company)

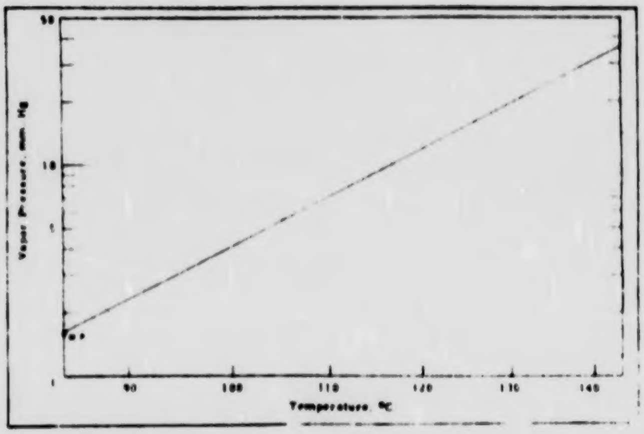


Figure 2. Vapor Pressure of Molten Acrylamide (Anon., 1969) (Reprinted with permission from American Cyanamid Company)

1% in acetic anhydride, nitroethane, dimethylformamide, dioxane, glycerol, acetonitrile, tetrahydrofuran, cresol, methyl ethyl ketone, pyrrolidone, triethanolamine, and dibutyl phthalate (Norris, 1967b). The molecular weight of a polymer is in part a function of the solvent in which the polymer forms; the less polar the solvent, the lower the molecular weight of the polymer (Wagner, 1968).

The solvent medium for polymerization may be any of the following (Bikales, 1973):

1) Water
2) Water and a water-miscible organic solvent
3) An emulsion of water and a solvent such as toluene
4) An organic liquid which is a solvent for the monomer

The greater the concentration of water miscible organic solvents, the less soluble the polymer which is produced, and hence, the easier it is to recover the polymer from the reaction medium. Recovery and drying of the pure polymer is, in fact, the most difficult and expensive part of the manufacturing process (Anon., 1969). However, water miscible organic solvents seldom make up more than a small fraction of the solvent medium, because the greater their concentration, the lower the molecular weight of the polymer. Since the major industrial application of polyacrylamides (flocculating agents) requires molecular weights to be as high as possible, water is the most common polymerization medium, with organic solvents used as precipitating and drying agents. Solvents are removed from the polymer by drum drying at elevated temperatures. Temperature control is important, since relatively high temperatures may have the effect of decreasing the molecular weight of the polymer and causing some cross-linking via imidization (Bikales, 1973). The overall manufacturing process must be optimized to obtain the desired requirements for a pure, dry, high molecular weight product, free of cross-linking.

The concentration of the monomer is kept low during polymerization to allow for adequate heat dissipation during the reaction. Also, high monomer concentration and/or high reaction temperatures lead to cross-linking, with consequent reduction of water solubility of the polymer (Thomas, 1964).

Free radical polymerization of acrylamide has been initiated by a variety of catalysts which include redox systems (Thomas, 1964), azo compounds (Cavell, 1962), peroxides (Dainton and Tordoff, 1957), X-rays and gamma-rays (Collinson _et al_., 1957), and anodic oxidation at a platinum electrode (Kunugi _et al_., 1972; Ogumi _et al_., 1974). The free radical mechanism of polymerization has been studied extensively (Dainton and Tordoff, 1957). The polymer chain is believed to go through several cycles of growth and rest before chain termination over a relatively long period of time ranging from several seconds to several minutes (Anon., 1969).

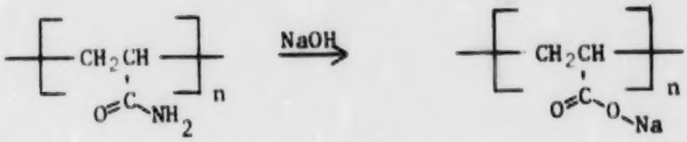
In addition to the previously-discussed factors affecting molecular weight of the polymer (i.e., temperature of reaction medium, concentration of monomer, etc.), the addition of specific amounts of 1-3 carbon aliphatic alcohols to the reaction medium allows a reproducible method of regulating (lowering) the weight average molecular weight of the polymer (Thomas, 1964).

The pH of the reaction medium also affects the nature of the polymer product. At or below pH 2.5, imidization occurs, resulting in a cross-linked, insoluble product (Anon., 1969). At pH 9 or higher, polymerization is accompanied by hydrolysis of the amide groups (Bikales, 1970). The presence of a strong base catalyzes polyamide formation (Breslow _et al_., 1957), which is particularly favored if an inhibitor for vinyl polymerization is also present

(Thomas, 1964). The product formed under these conditions is poly-ß-alanine (nylon 3), whose physical properties are quite different from polyacrylamide.

Acrylamide monomer does not have to be in solution in order to polymerize. When heated to its melting point, the pure solid may polymerize quietly or violently accompanied by the evolution of a great deal of heat, resulting in a highly cross-linked, insoluble gel. Polymerization in the solid state can also be made to occur at ambient temperatures and without violence by exposing acrylamide to ionizing radiation (Thomas, 1964). After removal of the monomer from the radiation source, polymerization continues for many months.

Polyacrylamide is nonionic. Polyelectrolytic character can be introduced where required for specific applications. Anionic character is introduced by partial hydrolysis of the amide groups by a strong base:



$$-\!\left[\mathrm{CH_2CH(C(=O)NH_2)}\right]_n\!- \xrightarrow{\mathrm{NaOH}} -\!\left[\mathrm{CH_2CH(C(=O)ONa)}\right]_n\!-$$

Modification of the polymer is possible either after its formation or during polymerization via the introduction of a suitable comonomer. Likewise, cationic character may be introduced either via a comonomer or through a post-reaction (Bikales, 1973).

Because acrylamide and its derivatives copolymerize with each other and with many other polar vinyl monomers, a wide variety of materials can be prepared via copolymerization. Solubility, softening temperature, viscosity, and elastomeric nature are some properties of the polymers which can be predictably modified by appropriate copolymer selection. A unique example of copolymerization in the recent literature involved gamma-ray induced graft copolymerization of acrylamide and acrylic acid to nylon 6 fabric (Trivedi et al., 1975).

In the presence of a homopolymer inhibitor, mixtures of acrylamide and acrylic acid were grafted to the fabric, considerably increasing its moisture retention without significantly affecting dyeability or tensile properties. In addition, the melting point of the grafted fabric was more than 100°C higher than that of the ungrafted fabric (m.p., 215°C).

The chemistry of the derivatives of acrylamide is very similar to that of the parent compound Polymerization of methacrylamide, for example, may be initiated in aqueous solution via an acidified bromate/thiourea free-radical producing redox system (Misra and Gupta, 1973). In general, acrylamide derivatives polymerize at a slower rate than acrylamide, and therefore, uncontrolled or spontaneous polymerization is less of a problem with the derivatives, reducing the need for inhibitors during storage and shipment. N-Methylolacrylamide, supplied as a 60% aqueous solution, for example, is considered very stable and is produced by at least one manufacturer without inhibitors (Proctor Chemical Co., 1975).

Cross-linked polyacrylamide is a rigid gel, insoluble in water and also impervious to the passage of water through it (Norris, 1967b). The exact properties of the gel are controlled by conditions of polymerization and the presence (or absence) of comonomers. American Cyanamid Company's chemical grout AM-9, for example, consists of a mixture of acrylamide and N,N'-methylenebisacrylamide. An aqueous solution of the monomeric mixture and a catalyst (β-dimethylaminopropionitrile and ammonium persulfate) are injected into soil formations. In a period of time which depends on the relative concentrations of the monomers and catalyst, polymerization takes place, sealing off the flow of water in the soil and binding the soil particles together (Norris, 1967b).

Molecular weights of polymers vary with preparation procedures as well as with the nature of the monomer; high molecular weight polymers are in general less soluble in water and have higher softening temperatures than low molecular weight polymers. High molecular weight polymers of acrylamide itself do form true solutions, but they are gels rather than fluids.

Substitution at the α-carbon of acrylamide tends to raise the softening temperature of the polymer, whereas substitution on the nitrogen tends to lower it. Branched alkyl groups as substituents tend to raise the softening temperature over corresponding derivatives with n-alkyl groups (Thomas, 1964).

Water solubility is retained through 3-carbon N-substituents. Solubility in acetone and 1-3 carbon alcohols increases as N-alkyl substituents increase to about 5 carbon atoms. Long alkyl chains confine solubility of the acrylamide compound to hydrocarbons (Thomas, 1964).

3. Properties of Commercial Materials

Table 3 lists commercial specifications for solid and solution acrylamide and selected acrylamide derivatives. The specifications in the table emphasize physical rather than chemical properties.

The wide variety of polyacrylamides commercially available testifies to the fact that manufacturers have considerable flexibility in designing products and modifying them to meet specific applications. Hercules Chemical, for example, produces under the trade name Hercofloc more than sixteen different acrylamide polymers in liquid and powder form, for industrial waste water applications. Typical specifications for the powder products are listed in Table 3.

4. Principal Contaminants in Commercial Products

Acrylamide is prepared commercially by two processes. The conventional "sulfate" process, which is rapidly declining in use, involves the hydration

Table 3. Acrylamide and Commercial Specifications for Selected Acrylamide Derivatives

(Prepared from Manufacturers' Product Data Sheets)

Acrylamide

	American Cyanamid	Vistron
Appearance	White, crystalline solid or pellet	
Assay, %	98.5 min.	98.0 min.
Water, %	0.8 max.	0.7 max.
Total iron as Fe, ppm	10.0 max.	10.0 max.
Water insolubles, %	0.02 max.	
Color of 20% solution, APHA	20 max.	20 max.
Butanol insolubles, %	0.2 max.	0.5 max.

Acrylamide, 50% aq.

	American Cyanamid	Vistron	Dow
Appearance	Clear, colorless to pale yellow solution	Clear liquid with yellow cast	Clear liquid with yellowish cast
Assay, wt. %	50±2	50±2	50±2
Inhibitor Cu^{+2}, ppm solids basis	25-30	30 max.	
pH	5.2-6.0	5.5-6.5	5.0-6.5
Stability	6 mo.	6 mo.	
Boiling point	105.5°C		99-104°C
Vapor press @25°C	19 torr		
Specific Gravity @25°C	1.04		1.04
Miscibility in water @25°C	All proportions		
Crystallization point	12-13°C		8-13°C

Methacrylamide

	White Chemical	Röhm, GmbH
Assay, %	98.4	98 min.
Water, %	1.0	1.5
Methacrylic acid	Not detected	0%
Ash, %	0.06	
Bulk density, lbs./ft^3	28.7	

N-*t*-octylacrylamide

	Proctor Chemical Company
Melting point, °C	58-63
Water, %	0.04
H_2SO_4, %	0.10
Acrylonitrile, %	nil
Diisobutylenes, %	0.10
Tetraisobutylenes, %	Trace
Solubility in 5% isopropanol	Soluble

N-Methylolacrylamide, 60% aq.

	Proctor Chemical Company
Appearance	Clear solution
Assay, %	60±2
Color, APHA	100 max.
pH	6.0-6.5
Formaldehyde, %	1.5-2.0

Polyacrylamide Powder (Hercofloc®)

	Hercules Chemical
Density, gm/ml	0.7
Particle size, %	25-35 through 200 mesh
Moisture, % (as packed)	15
pH (1% aq. sol.)	6.0 anionic, 8.5 cationic

of acrylonitrile (2-propenenitrile) with sulfuric acid monohydrate to form acrylamide sulfate. Various methods are used to separate the products (Carpenter and Davis, 1957). In a typical process, the sulfuric acid is neutralized with calcium oxide or ammonia. Calcium (or ammonium) sulfate is precipitated by concentrating and evaporating the solution under reduced pressure. The acrylamide is frequently removed by crystallization, although extraction with benzene or methanol has been reported (Bikales, 1970). Contaminants in the final product may include small quantities of acrylamide sulfate, calcium (or ammonium) sulfate, polyacrylamide (particularly if a polymerization inhibitor was not present during the hydrolysis), and/or traces of the inhibitor (such as Cu^{+2} or Fe^{+3}) if one was present.

A new commercial process involves the direct catalytic oxidation of acrylonitrile to the amide (Anon., 1973). The catalyst is metallic copper (Otsuka _et al._, 1975) or a fixed-bed copper-chromium combination (Anon., 1973). The reaction takes place in an aqueous medium, and the catalyst is conveniently removed by filtration (in a non-fixed bed system). Any unreacted acrylonitrile is removed by evaporation. The resulting aqueous solution of acrylamide can be sold as is, or the acrylamide separated from the water by evaporation and/or extraction with organic solvents and recrystallization. Either way, the acrylamide produced is of higher purity than obtained via the sulfate process. Total impurities (not including the solvent in aqueous solutions) are 0.1% or less (Otsuka _et al._, 1975); these include traces of iron and other metals, possibly acrylonitrile, and also ethylenecyanohydrin (from hydration of the carbon-carbon double bond of acrylonitrile instead of the cyano group). Since polymerization inhibitors are _not_ used, they are not a source of contamination of the product. There is also no possibility of contamination from sulfate salts in this process.

The principal contaminants of acrylamide polymers are the monomers. Although the polymers are generally considered to be nontoxic, the monomers are not. Polyacrylamides with which humans or their food will come in contact must have less than 0.05% residual acrylamide monomer in them (FDA, 1972 a).

B. Chemistry

1. Reactions Involved in Production and Uses

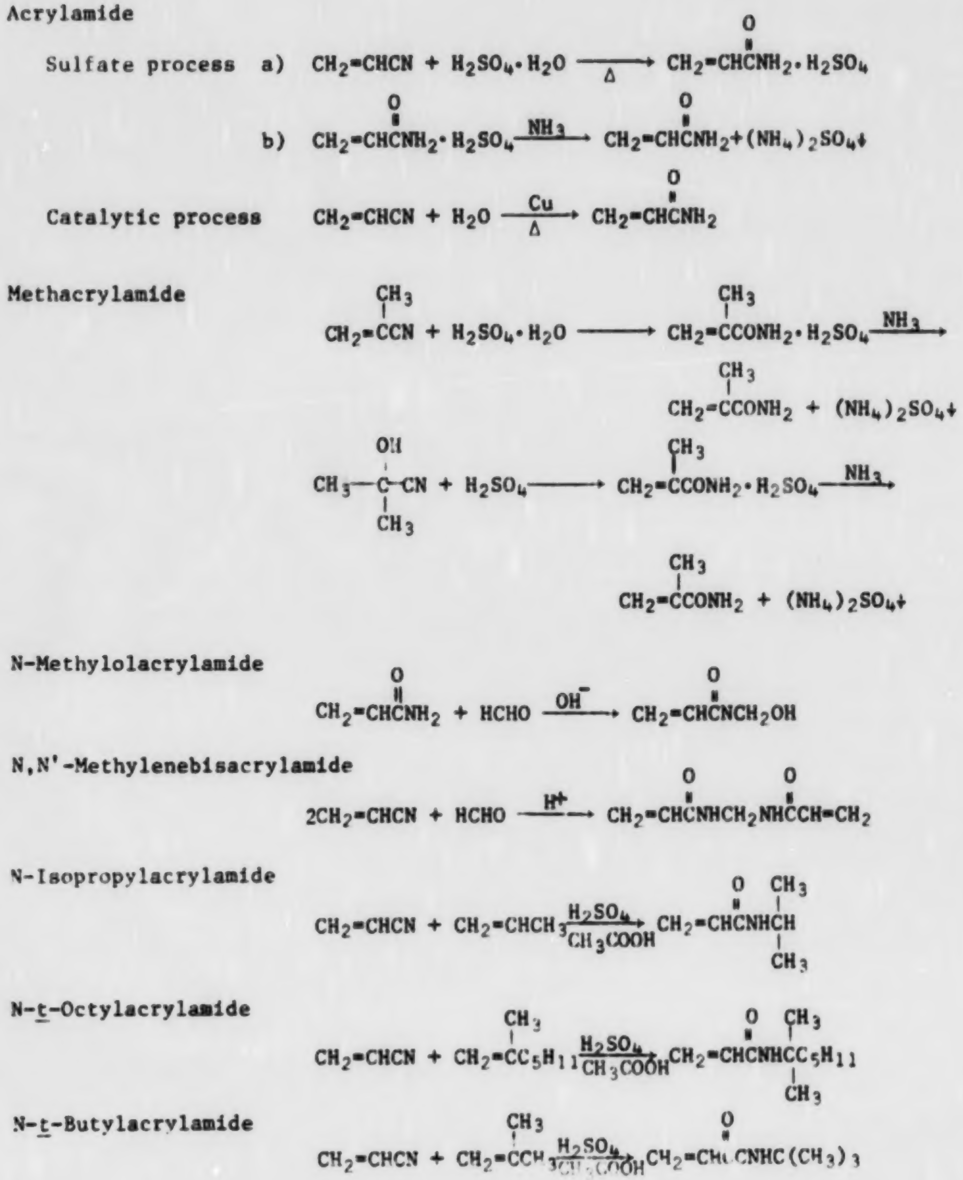
Synthesis of acrylamide begins with propylene, ammonia, and oxygen, which are reacted to form acrylonitrile. Acrylamide is produced from acrylonitrile as described above. Figure 3 shows the principal chemical equations for the production of acrylamide and its commercially significant derivatives.

Methacrylamide is prepared in an analogous fashion to acrylamide by the hydration of methacrylonitrile, and also via the decomposition of acetone cyanohydrin with sulfuric acid to give methacrylamide sulfate, which is then separated and purified by procedures similar to those used for acrylamide sulfate (Thomas, 1964).

N-Monosubstituted acrylamides having a secondary or tertiary alkyl carbon attached to the nitrogen are prepared via the Ritter reaction in which acrylonitrile combines with an olefin or alcohol in the presence of a strong acid (Plaut and Ritter, 1951). The other N-alkyl and N,N-dialkyl acrylamides are usually prepared by transamidation.

Acrylonitrile reacts with formaldehyde under acidic conditions in the industrial preparation of N,N'-methylenebisacrylamide (Bikales, 1970).

Acrylamide and its monomer analogs are considered to be thermally stable. The pure compounds are without unusual explosion or fire hazard when stored at room temperature (25°C). After three weeks of storage at 50°C, acrylamide shows no evidence of polymerization. After 24 hours at 80°C (just below the



Acrylamide

Sulfate process a) $CH_2{=}CHCN + H_2SO_4\cdot H_2O \xrightarrow[\Delta]{} CH_2{=}CH\overset{O}{C}NH_2\cdot H_2SO_4$

b) $CH_2{=}CH\overset{O}{C}NH_2\cdot H_2SO_4 \xrightarrow{NH_3} CH_2{=}CH\overset{O}{C}NH_2 + (NH_4)_2SO_4\downarrow$

Catalytic process $CH_2{=}CHCN + H_2O \xrightarrow[\Delta]{Cu} CH_2{=}CH\overset{O}{C}NH_2$

Methacrylamide

$CH_2{=}\overset{CH_3}{C}CN + H_2SO_4\cdot H_2O \longrightarrow CH_2{=}\overset{CH_3}{C}CONH_2\cdot H_2SO_4 \xrightarrow{NH_3}$

$CH_2{=}\overset{CH_3}{C}CONH_2 + (NH_4)_2SO_4\downarrow$

$CH_3-\overset{OH}{\underset{CH_3}{C}}-CN + H_2SO_4 \longrightarrow CH_2{=}\overset{CH_3}{C}CONH_2\cdot H_2SO_4 \xrightarrow{NH_3}$

$CH_2{=}\overset{CH_3}{C}CONH_2 + (NH_4)_2SO_4\downarrow$

N-Methylolacrylamide

$CH_2{=}CH\overset{O}{C}NH_2 + HCHO \xrightarrow{OH^-} CH_2{=}CH\overset{O}{C}NCH_2OH$

N,N'-Methylenebisacrylamide

$2CH_2{=}CHCN + HCHO \xrightarrow{H^+} CH_2{=}CH\overset{O}{C}NHCH_2NH\overset{O}{C}CH{=}CH_2$

N-Isopropylacrylamide

$CH_2{=}CHCN + CH_2{=}CHCH_3 \xrightarrow[CH_3COOH]{H_2SO_4} CH_2{=}CH\overset{O}{C}NH\overset{CH_3}{\underset{CH_3}{C}}H$

N-*t*-Octylacrylamide

$CH_2{=}CHCN + CH_2{=}\overset{CH_3}{C}C_5H_{11} \xrightarrow[CH_3COOH]{H_2SO_4} CH_2{=}CH\overset{O}{C}NH\overset{CH_3}{\underset{CH_3}{C}}C_5H_{11}$

N-*t*-Butylacrylamide

$CH_2{=}CHCN + CH_2{=}\overset{CH_3}{C}CH_3 \xrightarrow[CH_3COOH]{H_2SO_4} CH_2{=}CH\overset{O}{C}NHC(CH_3)_3$

Figure 3. Reactions Involved in Commercial Production of Acrylamide and Selected Analogs

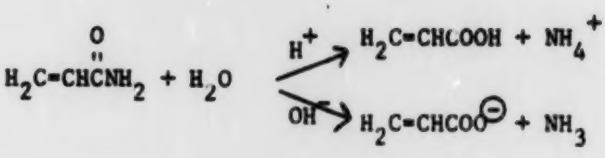
melting point), pure samples do not polymerize significantly (Anon., 1969). Above the melting point, however, acrylamide polymerizes spontaneously. The reaction is exothermic with the evolution of considerable amounts of heat (19.4 kcal/mole) (Anon., 1969). Contamination with suitable catalysts can also cause spontaneous polymerization regardless of the temperature. Under circumstances in which high temperatures cannot be avoided (as in the manufacture of acrylamide via the sulfate process, when the reaction medium is typically 90-100°C), or when it appears desirable to further stabilize solutions of acrylamide at moderate temperatures, polymerization inhibitors are employed. For example, to ensure the long-term stability of the 50% aqueous solution of acrylamide sold by American Cyanamid Company and Dow Chemical under similar specifications, Cu^{+2} is added to the solution (25-30 ppm), and it is kept saturated with oxygen by being constantly purged with air during storage (American Cyanamid Co., 1974; Anon., 1976 b). Runaway polymerization of solutions of this concentration would result in rapid boiling and consequently the generation of high pressures in the storage container.

Although stability data for acrylamide derivatives are not as complete as for the parent compound, in the pure form their stability is expected to be similar to that of acrylamide (Bikales, 1970). 2-Acrylamido-2-methylpropanesulfonic acid, for example, is stable at room temperature without the addition of any inhibitors or stabilizers. A 25% aqueous solution of this material (without stabilizer) shows evidence of polymerization after one month at room temperature and after one day at 50°C (Lubrizol Corp., 1974). N-Isobutoxymethylacrylamide, a liquid at room temperature, is stable in storage under normal conditions and shows no significant changes in viscosity or polymerization behavior after three months storage at 48°C (Anon., 1976 a). All acrylamide derivatives, are, however, subject to accelerated deterioration under conditions of prolonged exposure to heat, ultraviolet light, low pH, and other conditions favoring initiation of free radical catalyzed polymerization. A case of smoke, crackling, and small flames has been reported for four fiber drums containing N-methylolacrylamide (Coventry, 1965). Very small quantities of contaminants are believed to have catalyzed this reaction, and the material may have been stored at elevated temperatures. At the present time, N-methylolacrylamide sold in the United States is offered only in aqueous solutions.

Acrylamide readily polymerizes in the presence of free radicals under a wide range of conditions. In a typical industrial process, a 10-30% aqueous solution of acrylamide monomer in the presence of an appropriate catalyst at approximately 30°C yields linear polyacrylamide with molecular weights greater than 10,000,000. Recipes of this general description can be used to make products from about 500,000 daltons to over 10 million daltons by adjusting temperature, initiator, and monomer concentrations. Commercial polymers are frequently dried directly from the aqueous gel form and reduced to flake for sale. The polymerization reaction is carried out under a blanket of nitrogen with the solution purged with nitrogen to remove oxygen, a polymerization inhibitor (Anon., 1969). The pure polymer, recovered by precipitation and drying, is a white solid, usually in the form of beads, soluble in water, and insoluble in nonpolar solvents (Bikales, 1970). Substituents on the α-carbon have a greater effect on slowing the rate of polymerization than N-substituents.

2. Hydrolysis, Oxidation, and Photochemistry

Acid or base catalyzed hydrolysis of the amide groups of acrylamide to carboxyl groups yields acrylic acid or acrylate ion (Anon., 1969):



$$H_2C{=}CH\overset{O}{\overset{\|}{C}}NH_2 + H_2O \begin{cases} \xrightarrow{H^+} H_2C{=}CHCOOH + NH_4^+ \\ \xrightarrow{OH^-} H_2C{=}CHCOO^{\ominus} + NH_3 \end{cases}$$

Although polyacrylamide made in aqueous solutions is likely to have undergone some hydrolysis (Thomas, 1964), relatively severe conditions are required to completely hydrolyze solutions of acrylamide (see Table 4). In 0.5 N NaOH at 100°C, 90% of the acrylamide in a 10% solution is hydrolyzed within 12 minutes, but in a 0.03 N NaOH solution at 50°C, only 19% of the acrylamide in a 10% solution is hydrolyzed in 15.5 hours (Anon., 1969). The rate of hydrolysis of a 5% acrylamide solution in 0.5 M H_2SO_4 at 50°C is 0.9%/hour. Acid or alkali hydrolysis of polyacrylamide yields the corresponding salt or free acid of polyacrylic acid.

Table 4. Rates of Acid and Base-Catalyzed Hydrolysis of Acrylamide (Anon., 1969)

Initial pH	NaOH (Initial Normality)	H_2SO_4 (Molarity)	% Hydrolysis[a] 4 Hours	% Hydrolysis[a] 15.5 Hours	% Hydrolysis/Hour[b]
12	0.01		5.11	6.57	
12.3	0.02		10.30	13.35	
12.52	0.03		15.66	18.94	
0.70		0.1			0.3
0.00		0.5			0.9
-0.30		1.0			2.1
-0.70		2.5			4.5

[a] 10% Acrylamide solution at 50.8°C

[b] 5% Acrylamide solution at 50°C

Acrylamide, its derivatives, and their polymers are stable to air oxidation at ambient temperatures. Polyacrylamide and its solutions degrade at elevated temperatures, but the tendency to degrade is not dependent on the presence of an oxidizing atmosphere. Above 175°C, polyacrylamide undergoes imidization, releasing NH_3. Above 300°C, hydrogen gas and carbon monoxide are also released as degradation becomes more extensive (Anon., 1969).

Acrylamide absorbs light in the ultraviolet range from 200-280 nm (see Figure 1, p. 5), which is below the cutoff point for radiation from the sun at the surface of the earth. Acrylamide solutions in water do not polymerize on exposure to UV light, but acrylamide and N,N'-methylenebisacrylamide mixtures may be photopolymerized by visible light in the presence of a sensitizer or catalyst, such as riboflavin, silver salts, and metal oxides or sulfides (Anon., 1969). Hydrogen peroxide has been used to cause photosensitized polymerization of aqueous solutions of acrylamide (Dainton and Tordoff, 1957). One goal of photopolymerization investigations is to eventually develop a practical non-silver photographic process (Chaberek, 1965). This application of acrylamides is discussed further in the section on uses.

3. Other Chemistry

Several excellent reviews of the chemistry of acrylamide monomers are available (Bikales, 1970; Bikales and Kolodny, 1963; Anon., 1969). However, the only other chemical reaction, besides those described above, which appears to be relevant to environmental considerations is the bromination of acrylamide. The resulting addition product is used for analytical purposes (see Analysis and Monitoring, p. 48.).

II. Environmental Exposure Factors

A. Production and Consumption

1. Quantity Produced

The total production capacity of acrylamide monomer in the United States in 1974 is estimated to exceed 70 million pounds. The production of this much acrylamide would take about the same quantity of acrylonitrile starting material, which amounts to about 3% of the acrylonitrile produced in 1974 (Blackford, 1974). Annual production of acrylamide has been estimated to be 15-20, 30, 32, and 40 million pounds in 1966, 1969, 1972, and 1973, respectively (Blackford, 1974).

Production data for acrylamide derivatives are not available, but it is believed that they are all produced in significantly smaller quantities than acrylamide. In addition, many derivatives of acrylamide not mentioned in this report are undoubtedly produced in research quantities, but not in amounts of commercial significance at the present time. Blackford (1974) reported that diacetone acrylamide was produced in 10 million pounds per year, but the manufacturer (Lubrizol) has indicated that the compound is no longer produced.

In 1973, slightly less than 20 million pounds of polyacrylamide were produced in this country (U.S. International Trade Commission, 1973) (see Table 5). That is the latest year for which firm data are available. Because of increased manufacturing capacity for acrylamide monomer since 1973, polyacrylamide production for 1974 could be as high as 40 million pounds.

Table 5. Polyacrylamide Produced and Sold in the United States
(U.S. International Trade Commission, 1971-73)

Year	Quantity Produced (lbs.)	Quantity Sold	Value of Quantity Sold ($)	Average Cost per Pound ($)
1971	8,391,000	3,385,000	3,369,000	1.00
1972	19,106,000	14,418,000	12,377,000	0.86
1973	19,996,000	17,289,000	13,744,000	0.80

2. Producers, Major Distributors and Importers, Sources of Import, and Production Sites

Table 6 lists the current manufacturers of acrylamide monomer and their capacities as of April, 1974, as well as projected capacities based on announcements made in March, 1975, by the major producer, American Cyanamid Company. Table 7 lists those manufacturers who are producing acrylamide derivatives in commercially significant quantities. Most of the acrylamide monomer (and derivatives) manufactured by these companies is not sold, but is consumed internally by the acrylamide polymer manufacturers (see Table 8).

Table 6. Producers of Acrylamide Monomer
(Blackford, 1974)

Manufacturer	Capacities (million pounds) as of 4/1/74	as of 7/74	as of 1/77†	as of 3/77†
American Cyanamid Co. Industrial Chemicals Div. New Orleans (Fortier), Louisiana	40	50	80	90
Vistron Corp. (Subsidiary of Standard Oil of Ohio) Chemicals Department Lima, Ohio	15	15		
Dow Chemical Company USA Midland, Michigan	15	15		
Bio Rad Labs Richmond, California	*			

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*Data not available, but appears to be negligible fraction of the combined output of all producers (SRI, 1975; Blackford, 1974).

†Projected growth announced by company (Anon., 1975b).

Table 7. Producers of Acrylamide Derivatives

Manufacturer	Product	Source
Lubrizol Corporation Bayport, Texas	2-Acrylamido-2-methylpropanesulfonic acid	*
White Chemical Sales, Inc. Bayonne, New Jersey	Methacrylamide	*
Proctor Chemical Company Subsidary of National Starch and Chemical Co., Salisbury, North Carolina	N-*t*-Octylacrylamide N-*t*-Butylacrylamide N-Methylolacrylamide	* * *
American Cyanamid Company Organic Chemicals Div., Bound Brook, New Jersey	N,N'-Methylenebisacrylamide N-Isopropylacrylamide N-Isobutoxymethylacrylamide	SRI, 1975 SRI, 1975 *
Vistron Co.	N,N'-Methylenebisacrylamide	U.S. International Trade Commission, 1973

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* Industrial sources

Table 8. Producers of Acrylamide Polymers
(SRI, 1975)

Manufacturer	Location	Major Uses
American Cyanamid Company Industrial and Plastics Division	Linden, New Jersey	
Betz Laboratories, Inc.	Trevose, Pennsylvania	Water and waste treatment
Celanese Corporation Celanese Coatings and Specialty Chemicals, Subsidiary of Celanese Resins Division	Charlotte, North Carolina	
Dow Chemical USA	Midland, Michigan	
Hercules, Incorporated Coatings and Specialty Products Division	Hopewell, Virginia	Water and waste treatment

In 1969, the United States imported a total of 11 million pounds of various amides and imides, including some acrylamide from Japan. At the same time, over 200 million pounds of these compounds were manufactured domestically. The exact amount of imported acrylamide is not known, but it would appear to be a small fraction of domestic production (U.S. Tariff Commission, 1971).

3. Production Methods and Processes

Acrylonitrile is the major starting material required for all industrial methods for the manufacture of acrylamide. Acetone cyanohydrin or methacrylonitrile are used to produce methacrylamide.

Figure 4 shows the main steps involved in the sulfate (sulfuric acid) process for the production of acrylamide, with ammonia used as the neutralizing agent. Figure 5 is a flow diagram of the sulfate process including alternatives to ammonia neutralization which have or have had significant industrial use. The starting materials, acrylonitrile, sulfuric acid, and water, are usually mixed in equimolar quantities. Temperatures are typically kept around 100°C for the hydrolysis reaction, but some processes use higher temperatures, up to 200°C (Sittig, 1965). The hydrolysis reaction is strongly exothermic, necessitating temperature controls. Lower temperatures are generally preferred to minimize hydrolysis of the product as well as to prevent premature polymerization. It can be seen from the figures that isolation and purification of the acrylamide product is a major part of the sulfate manufacturing process.

The sulfate process will probably not be the main manufacturing process for acrylamide by the end of this decade. In 1971 the Dow Chemical Company began producing acrylamide via a new catalytic process suitable for directly hydrolyzing most organic nitriles to the corresponding amides ([illegible]n., 1973).

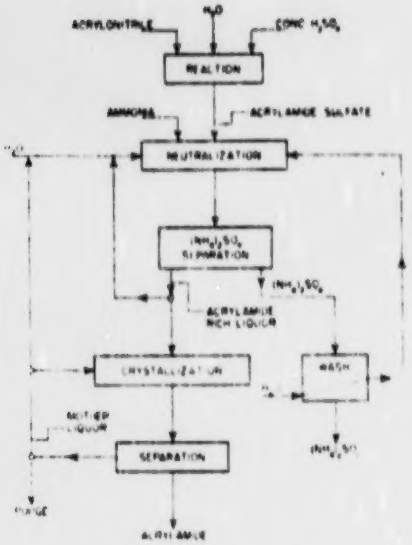

ACRYLONITRILE
H_2O
CONC H_2SO_4
REACTION
AMMONIA
ACRYLAMIDE SULFATE
NEUTRALIZATION
$(NH_4)_2SO_4$ SEPARATION
$(NH_4)_2SO_4$
ACRYLAMIDE RICH LIQUOR
CRYSTALLIZATION
WASH
MOTHER LIQUOR
SEPARATION
$(NH_4)_2SO_4$
PURGE
ACRYLAMIDE

Figure 4. Flowsheet for Sulfate Process for Acrylamide Production (Bikales and Kolodny, 1963) (Reprinted with permission from John Wiley & Sons, Inc.)

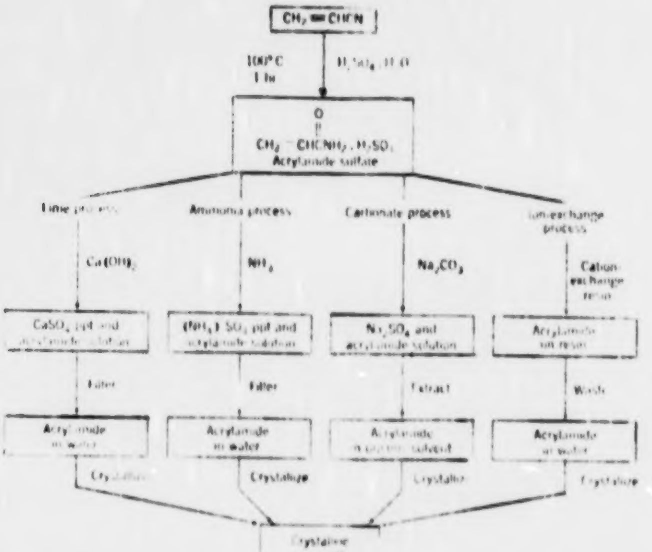

$CH_2{=}CHCN$
100°C
1 hr
H_2SO_4, H_2O
$CH_2{=}CHCNH_2 \cdot H_2SO_4$
Acrylamide sulfate
Lime process
Ammonia process
Carbonate process
Ion-exchange process
$Ca(OH)_2$
NH_3
Na_2CO_3
Cation exchange resin
$CaSO_4$ ppt and acrylamide solution
$(NH_4)_2SO_4$ ppt and acrylamide solution
Na_2SO_4 and acrylamide solution
Acrylamide on resin
Filter
Filter
Extract
Wash
Acrylamide in water
Acrylamide in water
Acrylamide in organic solvent
Acrylamide in water
Crystallize
Crystallize
Crystallize
Crystallize
Crystalline
$CH_2{=}CHCNH_2$

Figure 5. Variations on the Sulfate Process for Acrylamide Manufacture (Thomas, 1964) (Reprinted with permission from John Wiley & Sons, Inc.)

The catalyst consists of metallic copper and chromium oxide (Haberman and Tefertiller, 1971), which after several hours use is regenerated by treatment with a peroxide followed by reduction with hydrogen (Haberman, 1972). An outline of the process is shown in Figure 6. No waste stream is produced in this process; there are no byproducts. The process offers high yields (98.5+%) of acrylamide of high purity (99.5%) at a substantial fixed and variable cost advantage over the sulfate process. In the middle of 1974, the major producer of acrylamide monomer, American Cyanamid Company, completed a new plant at Fortier, Louisiana, capable of producing 10 million pounds per year of acrylamide monomer (Anon., 1975 b). This plant also uses a new process said to be free of pollution and byproducts because the acrylamide is made directly via hydrolysis of acetonitrile over a catalyst (Blackford, 1974). At the same time, the company announced plans to replace its 30 million pounds per year sulfate facility at Linden, New Jersey, with a 60 million pounds per year catalytic facility scheduled to go on stream in 1977 (Anon., 1975 c).

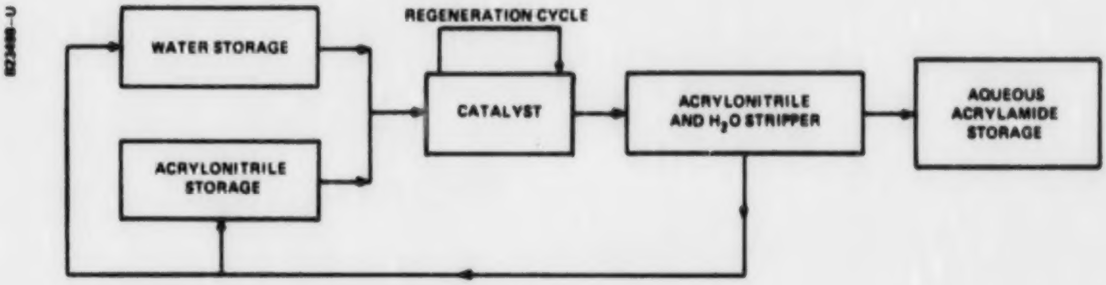


Figure 6. Catalytic Route to Acrylamide Eliminates Troublesome Byproducts and Increases Product Yields (Anon., 1973)

Figure 7 outlines the catalytic hydration process as developed by Mitsui Toatsu Chemicals, Inc., of Japan. The acrylonitrile is converted to acrylamide by a metallic copper catalyst mixed with the acrylonitrile and water. The optimum temperature of the reaction is 70-120°C, about the same as the temperatures typically used in the sulfate process. Unreacted acrylonitrile is removed by evaporation and the catalyst is removed (for reuse) by filtration. Very few by-products are said to form (Otsuka _et al_., 1975), so the aqueous acrylamide solution can be marketed or used internally with no further treatment or purification. Because the process is carefully controlled and the product is produced in a highly purified state, no polymerization inhibitors are added at any time. The manufacturer claims that the 30-50% acrylamide solutions marketed are stable and safe if stored in the original shipping containers and handled properly. Table 9 compares product specifications for acrylamide produced by the catalytic hydration process and the conventional sulfate process. The former process is capable of producing a product of higher purity at lower cost (because there are fewer steps), and the process is inherently by-product and pollution free.

Industrial methods for preparing other derivatives are discussed in Section I-B-1, p. 13).

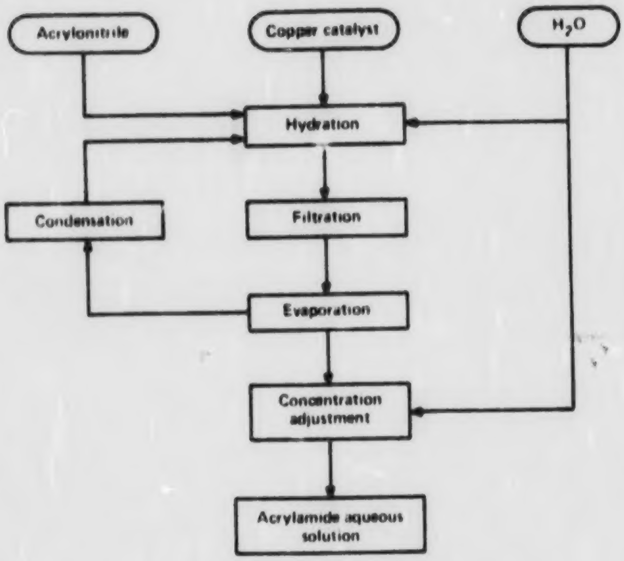

Acrylonitrile
Copper catalyst
H_2O
Hydration
Condensation
Filtration
Evaporation
Concentration adjustment
Acrylamide aqueous solution

Figure 7. Catalytic Hydration Process for Acrylamide Production (Otsuka *et al.*, 1975)

Table 9. Product Specifications (Otsuka *et.al.*, 1975)

Composition	Sulfuric Acid Method	Catalytic Hydration Method
Acrylamide %	99.0	99.9 (excluding water)
Water %	0.5	30-50% aqu. solution
$(NH_4)_2SO_4$	0.5	None
Iron and other %	Trace	Trace
Polymerization inhibitor %	Trace	None

4. Market Prices

Table 10 lists the current market prices for pure acrylamide monomer and selected derivatives and polymers. The price per pound for acrylamide (drum and tank quantities) decreased from 51¢ in 1962 to 34¢ in May, 1974 (Blackford, 1974). As of July 1, 1975, the price was back up to approximately the 1962 level. However, considering inflation, the effective price of acrylamide has decreased, and therefore, an increased interest in applications for this material may be anticipated.

Table 10. Current Market Prices for Acrylamide Products (Industrial Manufacturers)

Compound	Quotation	Basis	Manufacturer
Solid acrylamide crystals	50¢/lb.	50 lb. bags, full truckload or carload	Vistron
Acrylamide, 50% aqueous solution	41¢/lb. 100% basis; $115/drum	Tank trucks, cars, 55 gal. drums	Vistron
Methacrylamide	$1.75/lb.	55 lb. bags	White Chemical Sales
N-Isobutoxymethyl acrylamide	90¢/lb.	12 ton truck load	American Cyanamid
Various copolymers (anionic, cationic, or neutral)	$2.00-3.00/lb.	50 lb. bags or drums	Hercules

The price per pound of acrylamide sold in aqueous solutions is lower than that for the solid, because selling it in solution obviates the need for the costly processes of separating the acrylamide from the solution in which it is formed and drying the solid. Since the monomer is usually polymerized in aqueous solution, purchasing it in this form can save the buyer the trouble of handling the solid (i.e., problems of dust, etc.). Shipping costs for the solution are higher than for the solid, however. The greatest savings are therefore obtained when the point of consumption of the acrylamide is near the manufacturing plant.

5. Market Trends

Acrylamide production is estimated to have increased from approximately 30 million pounds in 1969 to 40 million in 1973 (Blackford, 1974), and this increase is expected to continue. For the period 1973-78, it is estimated that the average annual growth rate will be 8.5%, which will result in the production of approximately 60 million pounds in 1978 (Blackford, 1974). The major factors suggesting an expanding market for acrylamide are the use of polyacrylamides in water and waste treatment, and the expanding use of polymers in the oil industry to increase secondary yields (see Section II-B). The major factors which may tend to decrease the use of acrylamide are its toxicity and its potential as an environmental contaminant.

B. Uses

1. Major Uses

The major use of acrylamide and its derivatives is in the production of polymers and copolymers for various purposes.

Currently, the largest market for polyacrylamide is in sewage and waste water treatment, and this is estimated to have consumed 40% of the acrylamide produced in 1973 (Blackford, 1974). Polyacrylamides have also been approved for treatment of potable water by the USPHS Technical Advisory Committee on Coagulant Aids for Water Treatment as of September 28, 1961 (Anon., 1962). The amount of residual monomer allowed in such applications is 0.05% (Croll et al., 1974). Polyacrylamides make good flocculants because they are capable of forming electrostatic bonds with particles in a dispersed suspension (Morozumi, 1971). The activating points of hydrogen bond or coordinate bond formation between the suspended or dispersed particles and the polymer are the polar groups on the polymer. Therefore, these groups must not participate in significant inter- or intramolecular polymer hydrogen bonding. Polymer-polymer interaction is minimized in several ways:

1) Partial hydrolysis of the polymer chain results in chain extension which minimizes intramolecular association and maximizes cohesion of the suspended particles (Morozumi, 1971).

2) The concentration of the polymer is kept low, typically about 0.1%, in order to minimize intermolecular interaction (Morozumi, 1971).

3) The polymer dose can be lower if the molecular weight of the polymer is high. Since low polymer dose reduces intermolecular interaction, the molecular weights of the polymers are kept as high as possible (Anthony et al., 1975). An undesirable side effect of increasing the molecular weight of the polymer is that this decreases its solubility, but polyacrylamides are sufficiently soluble in water so that solutions of the required concentrations (ca. 0.1% or less) can be prepared from polymers ranging in average molecular weights from 10-20 million daltons.

4) Linear polymers have fewer intramolecular interactions than branched-chain polymers; therefore, linear polymers are more effective flocculants (Anthony et al., 1975). The atoms in branched-chain polymers are closer together than in linear polymers; hence they have more opportunity to interact. The linearity of a polymer is a function of the conditions under which it was formed. As a general rule, low monomer concentrations and low polymerization temperatures favor linear polymerization, while high monomer concentrations and high temperatures during polymerization favor formation of branched chains (see Section I-A, p. 1).

Acrylamide polymers are normally nonionic but can be produced in cationic or anionic forms when comonomers are used or by post reaction with appropriate reagents (see Section I-A-2, p. 8). Cationic copolymer flocculants are used for organic suspensions, low pH solutions, metallurgical processes, and as dewatering aids for concentrating slurries. Anionic copolymer flocculants are used in neutral and alkaline environments as thickening aids for dilute slurries (Floyd, 1975), and nonionic polymers find a wide and general flocculant use, especially in mining (Morozumi, 1971). Selection of the proper flocculant for a given application is an empirical process dependent upon the detailed laboratory examination of many variables (Hercules Corp., 1974).

The pulp and paper industry uses polyacrylamides as strengtheners and to aid in preventing fibers from being washed away (Moore, 1975). The residual acrylamide (and/or acrylamide derivative) content of paper and paperboard to be used in contact with aqueous or fatty foods is regulated by the Food and Drug Administration (FDA, 1974a) (see also Section I-A-4, p. 10). Pulp and paper uses accounted for approximately 20% of acrylamide consumption in 1973 (Blackford, 1974). The main uses of polyacrylamides in the paper industry are based on its flocculation activity and binding ability. Improved filler, pigment and fines retention and increased drainage rate are obtained by adding 20-60 lbs of alum per ton of fibre followed shortly by 1/4 - 1/2 lb of dissolved polyacrylamide per ton of fibre. The polymer is added to the fan pump or head box (MacWilliams, 1973).

2. Minor Uses

Besides the flocculant and pulp and paper applications, there are a number of minor uses of polyacrylamides. These uses are listed in Table 11 along with the major applications.

Table 11. Uses of Polyacrylamide (Thomas, 1964; Anon., 1969; MacWilliams, 1973)

Adhesives
Coal dust loss preventative
Coal flotation
Coating resins
Dental fillers
Drilling-fluid additives
Elastomer curing agent
Electrorefining improvement
Emulsion stabilizers
Flocculating agents for minerals, coal, sewage, industrial wastes, etc.
Flooding agents for petroleum recovery
Grouts for dams, foundations, tunnels, etc.
Hair sprays
Ion-exchange polymers
Leather-treating agents
Molding resins to increase strength, raise softening temperature, or to serve as plasticizing components
Paper additives and resins for faster draining, improved filler retention, coating, sizing, wet and dry strength improvements, etc.
Photographic films
Pigment-binding resins
Polyester laminating resins
Printing pastes
Propellant binders
Rodent repellants
Shaving creams
Soil stabilizers
Suspending agents
Textile resins for warp sizing, printing, shrinkproofing, antistatic treatments, binding nonwoven fabrics, improving dye receptivity, increasing dimensional stability of viscose rayon
Thickening agents
Tumor suppressants
Water clarifying, water-loss prevention in cements, waterproofing of masonry

Water soluble polymers, including polyacrylamides, are widely used in the petroleum industry. The polymers are used as flocculants in water recirculation systems (Huebotter and Gray, 1965), and they are also used for controlling the mobility of drilling fluids. One of the advantages of polyacrylamides in this application is their high resistance to biological attack under conditions prevailing in this application (MacWilliams et al., 1973). The main use of polyacrylamides in drilling fluids is in secondary oil recovery. Primary oil recovery ceases when natural underground pressures are reduced to atmospheric pressure by the removal of oil from rock or sand, which usually occurs after only 1/5 to 1/3 of the oil present has been removed. Secondary recovery may involve pumping water down behind the oil to generate sufficient pressure to keep the oil flowing. However, the masses of pumped water do not stay intact, but seeking the paths of least resistance, tend to form narrow streams through the oil/rock matrix and eventually emerge from the oil well along with the oil. Eventually the water/oil ratio becomes so high (20:1) that further use of the well becomes uneconomical (MacWilliams et al., 1973). The use of polyacrylamides (previously polymerized material) in water flooding inhibits streaming of the flood water and allows recovery of 50-100% more oil than would be possible using water alone (MacWilliams et al., 1973). This is possible because of a phenonmenon known as the "resistance effect" which is the apparent enhancement of the solution viscosity in porous media 5-20 times over the viscosity of the bulk solution (MacWilliams, 1973).

One of the few direct marketable uses of acrylamide monomer is in the production of chemical grouts and soil stabilizers for use in dams, foundations, and tunnel construction. The action of these materials has been described in Section I-A-2 (p. 9). In addition to American Cyanamid's AM-9 Chemical Grout, Nalco Chemical Company (Adams, 1966) has patented a mixture of acrylamide and methylenebisacrylamide in a slurry which is catalyzed in soil, sand, or clay to form a suitable cross-linked polymer, which stabilizes the soil matrix in which it forms. Similar monomer mixtures have been reported for use in sealing water leaks during underground construction (Miyazawa et al., 1973) and soil stabilization (Miki, 1973). A review of chemical grout materials for soil stabilization is available in the Japanese language (Higashimura, 1974). Industry sources have suggested that this market for acrylamide does not exceed 5% of the total production.

Acrylamide and its methylol derivative have been used in the textile industry to impart certain desirable qualities to fabrics, such as a durable press characteristic (Doshi and Varghese, 1971), which is obtained by grafting the monomer to the cellulose structure of the fabric (Doshi and Varghese, 1973). Acrylamide has also been used fo the preservation of interfibrillar hydrogen bonding in never-dried cotton (again by grafting the monomer to the cellulose fibers), which results in wet extensibility (ability to swell) several times that of untreated cotton (Williams et al., 1974).

Acrylamide undergoes photosensitized polymerization upon exposure to visible light in the presence of certain dyes (Delzenne et al., 1962), and this phenomenon has led to the investigation of acrylamide (and other monomers) as possible replacements for silver halide in certain photographic applications (Chaberek, 1965; Anon., 1975d). Photopolymers have been successfully used in holography (VanRenesse, 1972). In this application, photopolymers have an advantage over silver halides, because they do not need to be processed after exposure in order to obtain the hologram. Mixtures of acrylamide and N,N'-methylenebisacrylamide are of particular interest. These comonomers are the basis of a dye-sensitized system which has a longer photosensitive life than others investigated (Sugawara et al., 1975).

Polyacrylamide gels are used for a supporting medium in zone electrophoresis (Raymond and Weintraub, 1959). Electrophoresis in a gel of increasing polyacrylamide concentration allows the estimation of molecular weights of proteins (Margolis and Wrigley, 1975). In this relatively new technique, the porosity of the gel is controlled by varying the amount of cross-linking in the polymer. Cross-linking is a function of monomer concentration, and therefore, cross-linking tends to increase with high monomer concentration.

N-Isobutoxymethylacrylamide and other N-(alkoxymethyl)acrylamide derivatives have been used mainly as comonomers in the production of water insoluble protective coatings, fabric binders and finishing agents, elastomers, adhesives, and photographic emulsions (Anon., 1976 a).

Acrylamide derivatives, especially N,N'-methylenebisacrylamide, have been investigated as possible antitumor agents (Tomcufcik et al., 1961).

3. Discontinued Uses

Acrylamide sulfate was formerly used as an intermediate in the production of acrylic acid. This use was discontinued in 1972 when catalytic oxidation of propylene was shown to be lower in cost, to take fewer steps, and not to produce large quantities of by-product (ammonium sulfate) which had to be recovered (Blackford, 1974).

Diacetone acrylamide (MacWilliams, 1973) was used in formulating and molding low-pressure polyester decorative laminates, resulting in reduced cost and simplicity and speed of production over high-pressure laminating systems (Cech and Bretz, 1972). The only U.S. manufacturer of diacetone acrylamide, Lubrizol Corp., discontinued production in late 1975.

4. Projected or Proposed Uses

The wide range of uses acrylamide has been put to since its commercial production began in 1954 (Bikales and Kolodny, 1963) and the relatively short period of time it has been available in commercial quantities suggest that there may be additional applications, as yet undiscovered, in which acrylamide will serve. As for those uses which are current, acrylamide will undoubtedly remain important in sewage and waste water treatment in the future. Since many domestic oil wells are no longer capable of primary production, the demand for oil will probably make secondary recovery procedures (such as flooding) employing polyacrylamides more economically favorable than in the past. This is likely to be the area of greatest potential growth for acrylamide (Blackford, 1974).

5. Possible Alternatives to Uses

In the sewage and waste industry, polyacrylamides offer the advantage of retaining their water solubility even when very high molecular weight polymers are used. An equally effective substitute flocculant which is also biodegradable would be an excellent alternative to the non-biodegradable polyacrylamides. Such biodegradable flocculants were not noted in the literature that was examined.

The drilling industry employs a number of polymers besides polyacrylamides, including polyamines, polyacrylate salts, carboxymethylcellulose, hydroxyalkylcellulose, guar gum, and xanthum gum (MacWilliams *et al.*, 1973). While each polymer has usually been introduced for a specific purpose, their properties overlap to some extent. For example, all except the polyamines have been used in drilling applications. Therefore, if the use of polyacrylamide were discontinued in this field, substitutes are already available.

Polyacrylamides have been used in the applications listed in Table 11 (p. 31) because of their solubility in water, polar functional groups, low toxicity, and competitive cost. Similar results might be obtained in these applications if other polymers having like features can be found. For example, in applications involving low molecular weight polymers, polyacrylamides can be directly replaced by polymers of the methacrylic series with no substantial change in functional characteristics (Thomas, 1964).

C. Environmental Contamination Potential

1. General

Acrylamide end products contact the environment almost exclusively as polymers. However, a major exception is the use of acrylamide monomer in chemical grouts for dams, foundations, tunnels, etc. Acrylamide polymers usually contain some residual monomer which can escape into the environment at the point of use of the polymer product. Other sources of the monomers in the environment are from production, transportation, storage, polymerization, use, and disposal of the monomers. The actual quantities lost from any of these sources is unknown. However, the following sections will discuss the potential for such losses.

2. From Production

The environmental contamination potential from production depends on the particular production process considered. With the sulfate process, filters used in the separation steps are potential sources of environmental contamination unless they are treated to remove the residual monomer in them prior to being discarded. Likewise, solvents used for extraction and/or recrystallization of the pure monomer will contain residual monomer and may be a potential source of contamination if discarded rather than recirculated. The neutralization by-product (such as ammonium sulfate from the sulfate process) is also a potential source of trace amounts of the monomer.

While recrystallization is essential in the sulfate process in order to obtain a product of satisfactory purity, this is not so in the catalytic process. The acrylamide formed in the catalytic process may be eventually polymerized in the same aqueous solution in which it is formed, eliminating the processes of separation, recrystallization, handling the pure powder, and dissolving it again in water. Unlike the sulfate process, the catalytic process does not generate any by-product. Thus, the catalytic process has inherently fewer potential sources of environmental contamination (Otsuka et al., 1975).

Acrylamide and probably many of its derivatives are manufactured in closed systems which are not likely to be sources of environmental contamination (other than as described above), except in the event of a leak in the reaction vessel or pipes connected to it.

3. From Transport and Storage

Solid acrylamide is supplied in polyethylene-lined 5-ply bags containing approximately 50 pounds of crystalline powder. This method of packaging is not likely to lead to environmental contamination during shipping and storage as long as the integrity of the bag is maintained and the transportation and storage environments are free of heat sources which might cause violent spontaneous polymerization to occur.

Acrylamide solution (50% aqueous) is shipped in tank trucks built of Type 304 or Type 316 stainless steel, or in 55 gallon polyethylene-lined drums. Smaller volumes (1-5 gallons) are stored and shipped in molded polyethylene containers (American Cyanamid Co., 1974). Environmental contamination problems could arise through leaks in pipes, pumps, or tanks. Because acrylamide solutions must be constantly aerated while in storage to discourage polymerization (oxygen inhibits polymerization), small amounts of acrylamide could conceivably be removed from the tank with the air purge and thereby get into the atmosphere. However, the low vapor pressure of acrylamide would suggest that these losses are not very substantial.

In summary, it appears that the only way substantial amounts of acrylamide would be released to the environment during transport or storage would be by spills. No spills of acrylamide have been documented.

4. From Use

The overall use patterns and facile biodegradability of acrylamides would seem to preclude the likelihood of widespread environmental contamination. Localized problems are more likely such as in manufacturing environments (see Table 8, p. 21, for a list of producers and locations). In factories, there is the possibility of dust from empty containers of solid acrylamide and spray from solutions contaminating the surrounding air, floor, and walls of the building and clothes of persons in the manufacturing area. The residual contents of containers used to store and dilute solutions of acrylamide monomer, as well as to polymerize the monomer, and the water used to wash the containers are also sources of potential environmental contamination in the manufacturing facility.

Forty per cent of all polyacrylamides manufactured are used in water treatment as aids in increasing sedimentation rates and also as sludge dewatering agents. Residual monomer in the polymers would be likely to leach out into the water and be present in the processed water, subject, of course, to prior or consequential chemical or biological degradation. Should the processed water reach end users prior to chemical or biological removal of the acrylamide, its presence could present a hazard. There are no data as to how much acrylamide is placed in the environment from this use, nor is a reliable quantitative estimate easily established. At the concentrations at which polyacrylamides are typically used in water processing (a few percent), the concentration of the residual monomer in the water would be very low (roughly an order of magnitude less than the dissolved polymer). It is, therefore, expected that any residual monomer present in the polymer is not likely to precipitate out in the sludge, but would appear in the processed water output. This is supported by the work of Croll et al. (1974) who found that the acrylamide content present in two sewage sludge samples that had been conditioned (sludge settling and filter pressing) contained less than 0.1 μg/ℓ. Croll and coworkers (1974) further examined seven sludge samples to determine the acrylamide recovered in the effluent. The recovery varied from 13 to 100% depending upon the sample and the sludge concentration procedure (filter pressing, settling, or freezing). The recovered water from the dewatering procedure may be returned to the water treatment process or disposed of as an effluent (Croll et al., 1974), the latter being a source of acrylamide release.

About 20% of all polyacrylamides manufactured are used in the pulp and paper industry directly in paper manufacturing to impart certain desirable physical characteristics to the fibres, as well as in waste water treatment. In these uses, contamination of water could result from the leaching of monomer in the polymer, exactly as in the use described in the previous paragraph. Monitoring data have demonstrated the presence of acrylamide in paper mill effluents (Croll et al., 1974).

As in the above two uses, the potential contamination of the environment with acrylamide in oil well secondary recovery flooding techniques also involves the possibility of residual monomer in the polymer leaching into the immediate vicinity of the well, which, in this case, might possibly involve migration into groundwater supplies if prior chemical or biological degradation did not take place. The likely increased use of polyacrylamides in oil production increases the risk of contaminating the surrounding areas and possibly local aquifers.

Chemical grouts containing acrylamide monomer (less than 5% of the total acrylamide production) are applied in such a way that the monomer has direct contact with soil. Any residual monomer that has not polymerized during the soil stabilization step in dams, tunnels, etc., could leach into the surrounding soil and eventually into water. Such an incident has been reported by Igisu et al. (1975) where acrylamide was used as a chemical grout near a family well. Also, these grouts present an occupational hazard to the personnel using the material. This is the major use in a non-manufacturing environment which could give rise to serious, although restricted, acrylamide poisoning incidents in humans.

In summary, the major usage source of environmental contamination potential of acrylamides is residual monomer in the polymers, especially when they are used in food processing, waste water treatment, food container manufacturing, pulp and paper processing, and other applications where residual monomer may come into direct contact with water.

5. From Disposal

Potential disposal sources of acrylamide include the residues in reaction vessels used for its manufacture, pipes used for transport of solutions of the monomer, empty bags used for transport and storage of the solid, and empty tanks, trucks, and drums used for transporting solutions of the monomer. The acrylamide residues in these sources may be decontaminated by catalytic polymerization (see Section II-D-3, p. 46) prior to discarding the containers or equipment. Polymerization should take place before these items are rinsed with water which flows directly into a sewer whose effluent is not treated to remove acrylamide. The Dow Chemical Company recommends biological degradation as the procedure of choice for detoxification of disposed acrylamide, whenever facilities for this type of disposal are available (Anon., 1976 b). Biodegradation is preferred because of the risk that polymerization will not proceed to completion When chemical detoxication is necessary, the use of 20% sodium sulfite in excess is recommended. This reagent reacts with acrylamide to form β-sulfoacrylamide, a compound of demonstrated low toxicity (MacWilliams, 1976).

Croll *et al*. (1974) studied the effectiveness of various water treatment processes in the removal of acrylamide from samples of water from the River Thames. Table 12 summaries the results of their study. Filtration methods and the usual chlorination a. pH ∿ 8 were shown to have no practical effect on the concentration of acrylamide. Thus, it appears that if acrylamides are released into waste waters while being used as flocculants, they will not be removed by physical or chemical methods. Of the chemical techniques explored, the most efficient and the safest is probably the treatment of the water samples with 3 mg/l ozone. On the other hand, Croll *et al*. (1974) have demonstrated that acrylamide is biodegraded, and therefore, if a biological process is used subsequent to flocculant treatment, the amount of acrylamide released will probably be very small.

Table 12. The Effect of Some Water Treatment Processes on 6 $\mu g\ l^{-1}$ Acrylamide (Croll *et al*., 1974)

Treatment	Quantity mg l^{-1}	pH	Contact time (h)	% Acrylamide removed
$KMnO_4$	1	5.0	4	100
$KMnO_4$	1	8.5	4	100
MnO column		5.0	0.1	17
MnO column		7.0	0.1	33
Ozone	3	7.0	0.5	100
Cl_2	10	1.0	4	100
Cl_2	10	5.0	4	64
Cl_2	10	8.5	4	nil
Active carbon	8	5.0	0.5	13

6. Potential Inadvertent Production of the Chemical in Other Industrial Processes as a By-Product

Industrial processes, other than those involving direct production of acrylamide and its derivatives, are not, in general, likely to produce a vinyl-amide by-product because of the relative chemical reactivity of the monomer and specialized conditions necessary for the formation of this type of compound. The following reagents and conditions have been shown to result in the production of acrylamide (MacWilliams, 1973) but are not known to be found in commercial processes:

a) Acrylyl chloride and ammonia at low temperatures

b) Acrylic anhydride and ammonia

c) Acrylyl isocyanate and water

d) Acetylene and carbon monoxide in the presence of ammonium hydroxide and iron and nickel carbonyls

e) Thermal decomposition of β-hydroxy, β-dialkylamino, or β-alkoxypropionamides in the presence of silica, calcium oxide, or other suitable catalysts

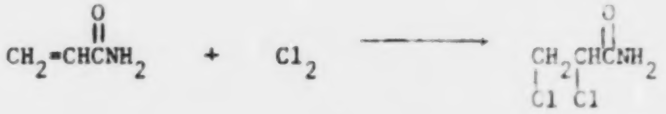
f) Dehydrohalogenation of a β-halopropionamide in the presence of a base

g) Pyrolysis of α-acetoxypropionamide

h) Neutralization and heating of ethylene cyanohydrin-sulfuric acid adduct after reacting with ammonium sulfate or ammonia

7. Potential Inadvertent Production in the Environment

The major potential source of environmental contamination by acrylamide is from its release into the environment after being produced elsewhere. There is no evidence that acrylamide or its commercially significant derivatives are, or are likely to be, directly produced in the environment. However, this does not preclude the possibility of the production of noncommercial derivatives. For example, acrylamide rapidly undergoes halogenation of its double bond; this is in fact used as a means of quantitatively assaying the pure compound (see Section II-E-1, p. 48). Since acrylamide passes through water treatment plants employing chlorination (see Section II-C-5, p. 40), it is possible for the acrylamide eventually to undergo halogenation in the chlorinated water to form 2,3-dichloropropionamide:



$$CH_2{=}CH\overset{\overset{O}{\|}}{C}NH_2 \quad + \quad Cl_2 \longrightarrow \underset{Cl}{CH_2}\underset{Cl}{CH}\overset{\overset{O}{\|}}{C}NH_2$$

Croll et al. (1974) have demonstrated that, under acidic aqueous conditions, sizable quantities of acrylamide are removed by chlorination.

D. Current Handling Practices and Control Technology

1. Special Handling in Use (American Cyanamid, 1974)

Acrylamide does require special handling for safe use and can cause serious health problems if handled carelessly. Clean work clothing should be worn daily, consisting of a head covering, long sleeves and pants, impervious gloves of rubber or plastic, and rubber footwear. Spills of acrylamide solution on clothing or the contamination of clothing with solid acrylamide requires immediate removal of the affected clothing followed by laundering before reuse. Gloves should be washed thoroughly before removal and discarded if contaminated on the inside. Work clothing should never be worn home and workers should shower before changing into fresh clothing.

The handling of acrylamide in ways that may create dust from the solid or spray from solutions should be avoided, if possible. When dust or spray is unavoidable, goggles and respirators should be worn (see Table 13).

Table 13. Respirators Suitable For Work With Acrylamide (American Cyanamid, 1974)

Name	Model	Cartridge/Filter	Manufacturer
Glendale	GR-2021	C-21/F-10	Glendale Optical Company, Inc. 130 Crossways Park Drive Woodbury, New York 11797
A.O. Respirator	R-5055	R55	American Optical Company Southbury, Massachusetts 01550
Wilson Respirator	841CD	41/R415	Wilson Products Division of Ray-O-Vac Co. Reading, Pennsylvania 19605

Dust or spills on exposed skin require immediate flushing with plenty of water. Food, beverages, tobacco, magazines, newspapers, and other material that will be eaten or intimately handled should never be used in the acrylamide work area. Before eating in a non-work area,workers should wash their hands thoroughly. Spills should be promptly cleaned and the entire work area decontaminated at least once a week. Empty containers should be isolated and then buried in an approved landfill or incinerated. Drums may be reused if washed up under carefully controlled conditions (Anon., 1976 b).

2. Methods of Transport and Storage

Solid acrylamide is shipped in multi-wall moisture-proof bags containing approximately 50 pounds each, in lots of 24,000 pounds per truckload or 30,000 pounds per carload (Vistron, 1975).

Acrylamide solution (50% aqueous) is shipped in tank trucks made of either Type 304 or 316 stainless steel, lined tank cars, or in 55 gallon drums consisting of a polyethylene insert (DOT-2SL Spec.) overpacked in a fiber drum (DOT-21P Spec.). Smaller samples are shipped in 5 gallon blow-molded polyethylene containers with 2" screw caps overpacked in a strong fiber box, and in one-gallon glass jugs with plastic screw caps and polyethylene liners. Each jug is overwrapped with two 4 mil polyethylene bag liners, tied off, and inserted in a strong fiber drum. Adequate cushioning is required during transportation for acrylamide solutions shipped in glass jugs (American Cyanamid, 1974). The Dow Chemical Company prefers the use of steel drums (DOT 37M) over fibre drums for bulk shipments because of the greater resistance to accidental holing by fork lift trucks. Also, Dow limits shipment of 50% aqueous acrylamide in glass containers to specially packed pint bottles (Anon., 1976 b).

Drums, glass jugs, and polyethylene containers should not be filled to more than 85% of capacity to allow for a supply of air sufficient to inhibit polymerization. Storage temperatures should not exceed 100°F. Direct sunlight must be avoided, as should any other significant heat source. In the case of solutions, the storage temperature should not be allowed to fall below 60°F. American Cyanamid (1974) recommends that all solutions be dated and not stored longer than six months before use.

Bulk storage tanks for acrylamide solutions should not be filled to more than 75% of their capacity. Bulk tanks must have provision for continuous air purging with approximately 1/2 cubic foot per minute per 1000 gallons capacity. The air must be instrument grade (clean) and monitored for temperature and flow. The pH of the solution should be monitored also, and adjusted if necessary to the range 5.2 - 6.0 for optimum inhibitor effectiveness. All tanks and lines must be insulated and temperature controlled with water. The storage tank should be surrounded by a concrete dike capable of containing the entire volume of the tank should it rupture. Provision must also be available for the rapid addition of a polymerization inhibitor (such as copper sulfate pentahydrate, 4 pounds per 1000 gallons 50% acrylamide solution) and cold water, in the event that unexpected polymerization should commence. Also, a facility for rapid mixing of the cold water, copper sulfate, and monomer solution should be available. An example of a typical storage facility recommended by the Dow Chemical Company is shown in Figure 8.

3. Disposal Methods

Rinse water containing acrylamide and surplus acrylamide solution must be treated prior to disposal in a sewer or landfill. The recommended treatment (American Cyanamid, 1974) is to add to every 12.5 gallons of the waste solution 0.4 pounds potassium or ammonium persulfate dissolved in a minimum amount of water, followed by 0.2 pounds sodium bisulfite dissolved in a minimum amount of water. After allowing two hours for polymerization to take place, the waste solution may be disposed of in a sewer or landfill. An alternate method for disposal is biodegradation, which is preferred by Dow Chemical where available because of the risk of failing to chemically polymerize all of the monomer (see Section II-C-5, p. 40).

4. Accident Procedures

In the event of accidental physical exposure to acrylamide, such as contact of the solid or solution with the skin, the individual involved should discontinue exposure as soon as possible, immediately irrigate the affected area thoroughly with plenty of water, and seek the advice of a physician. Speed of action in washing is important (American Cyanamid, 1973).

Persons dealing with accidental spills of solid or solutions of acrylamide should protect themselves with proper dress and respirators (see Section II-D-1, p. 43). Solid spills may be swept up and placed in a metal container prior to incineration, although dust may be a problem. Liquid spills should be covered with an absorbent material which can be swept up and placed in

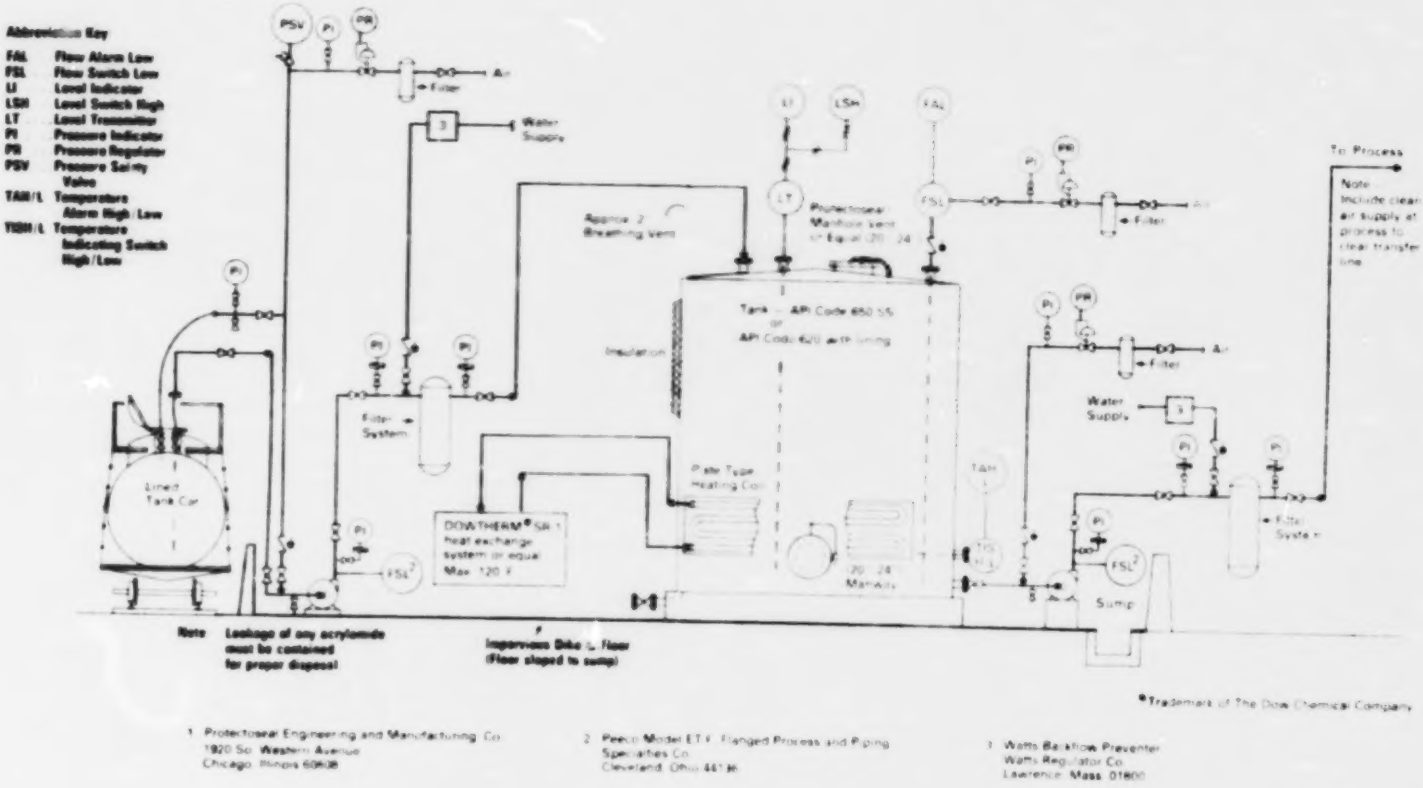

Abbreviation Key
FAL Flow Alarm Low
FSL Flow Switch Low
LI Level Indicator
LSH Level Switch High
LT Level Transmitter
PI Pressure Indicator
PR Pressure Regulator
PSV Pressure Safety Valve
TAH/L Temperature Alarm High/Low
TISH/L Temperature Indicating Switch High/Low
PSV
PI
PR
Air
Filter
3
Water Supply
PI
PI
PI
Filter System
Approx. 2" Breathing Vent
Insulation
LI
LSH
FAL
LT
Protectoseal Manhole Vent or Equal (20"-24")
FSL
PI
PR
Air
Filter
Tank – API Code 650 SS or API Code 620 with lining
PI
PR
Air
Filter
Water Supply
3
PI
PI
PI
Filter System
To Process
Note: Include clean air supply at process to clear transfer line
Lined Tank Car
DOWTHERM® SR-1 heat exchange system or equal Max. 120°F
Plate Type Heating Coil
PI
FSL^2
TAH
TIS H/L
20"-24" Manway
PI
FSL^2
Sump
Note: Leakage of any acrylamide must be contained for proper disposal
Impervious Dike & Floor (Floor sloped to sump)
®Trademark of The Dow Chemical Company
1. Protectoseal Engineering and Manufacturing Co. 1920 So. Western Avenue Chicago, Illinois 60608
2. Peeco Model ET-F, Flanged Process and Piping Specialties Co. Cleveland, Ohio 44136
3. Watts Backflow Preventer Watts Regulator Co. Lawrence, Mass. 01800

Figure 8. Recommended Unloading and Storage Facility for 50% Aqueous Acrylamide Solutions (Anon., 1976 b) Copyright 1976. The Dow Chemical Company. Reproduced with permission.

a suitable container for disposal by incineration. Residues on floors and equipment should be treated with 3 gallons/sq. ft. 1.6% potassium persulfate solution followed immediately by an equal volume of 1.6% sodium metabisulfite solution. The mixture of catalysts, after standing for 30 minutes, may be rinsed down a floor drain with generous quantities of water.

5. Current Controls and Technology Under Development

Although no definite data are available on this matter, it is assumed that those who manufacture, transport, and use acrylamide are aware of its hazards and use proper handling techniques in most cases. Monitoring techniques for the determination of acrylamide in air have been developed by American Cyanamid (1974) and Dow Chemical Company (1976). Presumably these are in use in industrial environments.

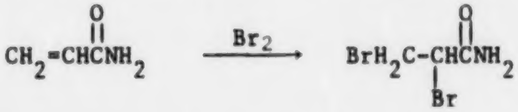
E. Monitoring and Analysis

1. Analytical Methods

There are many chemical and instrumental techniques available for the analysis of acrylamide. As may be expected, the suitability of each varies with the particular application required. Analysis of the monomer for purity, of the polymer and products made from the polymer for residual monomer, of waterways for trace amounts of acrylamide, and of the blood or urine of workers exposed to acrylamide are typical assay problems for this material. The discussion below includes current analytical techniques and their application to these problems.

Acrylamide may be purified by sublimation of the solid under reduced pressure, recrystallization from a solvent such as benzene, or via ion exchange of aqueous solutions. The usual elemental procedures may then be used to determine C, H, N, and O. An infrared absorption spectrum and, if necessary, qualitative tests for unsaturation and the presence of the amide group confirm the identification of the compound.

Several procedures may be used to determine the purity of acrylamide as the commercial product. Probably the most widely used is the "bromate-bromide" method, which depends upon the ease with which acrylamide undergoes addition reactions at the α,β unsaturation as a result of the electron-withdrawing character of the amide group. In this method, acrylamide reacts stoichiometrically with excess bromine generated by an acidified bromate-bromide solution. The unreacted bromine is then converted to bromide by the addition of excess iodide, and the liberated iodine is back-titrated with standardized thiosulfate using a starch indicator (Anon., 1969). A reagent blank must be run, since this is a difference method. The method works not only for acrylamide, but also for N,N'-methylenebisacrylamide and methacrylamide, and, therefore, each of these three compounds interferes with assays for the others. The method does not work for N-isopropylacrylamide, N-methylolacrylamide, or diacetone acrylamide (MacWilliams, 1973). Other interferences include acrylic acid, ethyl acrylate, and other olefins. The precision of the method is about ±0.3% (Norris, 1967 a).



$$CH_2{=}CH\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow{Br_2} BrH_2C{-}\underset{Br}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}NH_2$$

The D.C. polarographic method is highly specific for acrylamide, but has lower precision (±1%) than the preceding method (Norris, 1967 a). A two electron reduction corresponding to the formation of propionamide occurs at -1.90 volts vs. a saturated calomel electrode in 0.1 M tetramethylammonium hydroxide in 30% ethanol-water solution (MacWilliams, 1973). Acrylonitrile interferes with this technique (Norris, 1967 a), which is primarily a trace method rather than a method meant for routine assay.

Trace amounts of acrylamide in polyacrylamide can be detected to less than 1 ppm via differential pulse polarography (Betso and McLean, 1976), which is more sensitive than conventional D.C. polarography. Although ethyl acetate interferes with this technique, acrylic acid and acrylonitrile do not.

Techniques which are less commonly used include morpholine addition, for which a precision of 0.1% has been reported (other unsaturated compounds interfere), and nonaqueous titration of acrylamide in nitromethane with standard perchloric acid, for which a precision of 1% is estimated (other compounds of comparable base strength interfere) (Norris, 1967 a).

A spectrophotometric technique, involving the reaction of acrylamide with diazomethane to give a stable 2-pyrazoline, which produces an intense color on reacting with 4-dimethylaminobenzaldehyde or 4-dimethylaminocinnamaldehyde, has been used to estimate acrylamide concentrations in urine (Mattocks, 1968). The technique is linear over a range of 50-200 μg acrylamide per milliliter of urine.

The Food and Drug Administration has set a maximum level of 0.05% (500 ppm) as an acceptably safe level for residual acrylamide monomer in polyacrylamide used in processing beet and cane sugars (FDA, 1972 c) and in paper goods in contact with food (FDA, 1974 a). The same standard is applied to polymers used for clarification of potable water in England (Croll and Simkins, 1972) and in this country (Spencer and Schaumburg, 1975). Methanol-water (4:1) solution has been found to be an efficient quantitative extractant for acrylamide monomer from polymers and copolymers (Croll, 1971). Flame ionization gas chromatography has been used to analyze the polymer extracts without further preparation. The sensitivity of the technique is 0.004% acrylamide in polymer or 40 ppm. Acrylic acid does not interfere.

American Cyanamid (1974) has used flame ionization gas chromatography in the determination of acrylamide in air. A minimum of 10 cubic feet of air is sampled in a two hour period. The acrylamide is extracted with water which is then diluted with methanol prior to injection into the gas chromatograph. No data are given on sensitivity, which would depend upon the actual size of the sample used for the assay. The Dow Chemical Co. has also developed a method for determination of trace amounts of acrylamide in air (Anon., 1976 d). The acrylamide present in samples is retained in an aqueous solution. Interferences are removed with mixed-bed ion exchange resins and the acrylamide determined via differential pulse polarography (electrochemical reduction of the double bond). Five to 200 μg of acrylamide can be determined per ten mℓ of aqueous solution.

An electron capture gas chromatographic assay has been developed which is much more sensitive (0.1 ppb) than flame ionization gas chromatography (Croll and Simkins, 1972). This method was developed to detect acrylamide in water levels down to 0.1 μg/l. The high sensitivity is achieved by bromination of the acrylamide to α,β-dibromopropionamide which can easily be quantitatively extracted from aqueous solutions with organic solvents. High volatility solvents are selected so that the extract can be concentrated without losing the brominated solute. Acrylamide itself is very difficult to extract from aqueous solutions and tends to escape when such extracts are concentrated by evaporation.

Acrylamide monomer can be easily and quickly determined in samples of pure aqueous solutions by means of measurement of the refractive index of the solutions (Anon., 1976 c). The method offers 0.4% absolute reproducibility (at 95% confidence) and is suitable for solutions ranging in concentrations from 5-50%.

Differential thermal analysis, a qualitative technique, has been used to characterize polyacrylamides used as flocculating and dispersing agents (Concilio and Jahnke, 1972). Anionic, cationic, and neutral polymers could be distinguished from each other and from polyacrylic acid with this technique, and hydrolysis products of polyacrylamide could be identified. The concentrations of polymers in the aqueous solutions studied were about 1%.

The analytical techniques described above are summarized in Table 14.

Table 14. Summary of Assay Techniques Applicable to Acrylamide

Name	Approximate Sensitivity	Application	Interferences	Reference
Refractive Index	50,000 ppm	Quality control	Anything affecting refractive index	Anon., 1976 c
Bromate-bromide	1,000 ppm	Assay commercial product	Unsaturated compounds	Anon., 1969
D.C. Polarography	10 ppm	Assay commercial product; detect trace levels	Alkali cations in above trace levels, acrylic esters	Norris, 1967 a
Colorimetric	0.1 ppm	Urinalysis; detect trace levels; assay commerical product	Aldehydes, ketones, pyrroles, indoles, hydrazine, aromatic amines	Mattocks, 1968
Flame Ionization Gas Chromatography	40 ppm	Monomer in polymer	Polymer extract may have to be further purified via TLC	Croll, 1971
Differential Pulse Polarography	> 1 ppm	Trace levels, monitoring industrial environment	Acrylonitrile, acrylic esters, alkali cations	Betso and McLean, 1976
Electron Capture Gas Chromatography	0.1 ppm	River water; trace levels		Croll and Simkins, 1972

2. Current Monitoring

In England, the acceptable concentration of 0.05% acrylamide monomer in polyacrylamide being used for potable water treatment applies where the average polymer dose to the water does not exceed 0.5 mg/l (in the U.S. 1 mg/l is the standard) (Croll et al., 1974). This corresponds to a highest acceptable average level of acrylamide in potable water of 0.25 μg/l and a maximum short-term level of 0.5 μg/l. Croll and his coworkers (1974) monitored industrial effluents and sludge conditioning works to determine if these levels were being maintained. They also explored the biodegradation of acrylamide in river water and sewage effluent, and the possibility that acrylamide might be removable from water supplies by commonly employed processes, such as chlorination, charcoal filtration, etc. (see Section II-C-5, p. 40 and III-A-1, p. 56).

The results of analyses of industrial effluents are summarized in Table 15. All the plants that were monitored employed polyacrylamide or acrylamide-acrylic acid copolymers as flocculating agents, and without exception, all discharge acrylamide into the environment in amounts which far exceed the maximum allowed levels for potable water. In the case of the clay pit, the concentration of acrylamide in the receiving stream was 1.2 μg/l. Further downstream at a waterworks intake the level dropped to 0.3 μg/l, which is still above the average permissible level for drinking water.

Table 15. Concentrations of Acrylamide in Some Industrial Effluents (Croll, *et. al.*, 1974)

Effluent	Acrylamide concentration $\mu g\ l^{-1}$
Coal mine A tailings lagoon	42
Coal mine B tailings lagoon	39
Coal mine C coal washing effluent lagoon	1.8
Coal mine/coking plant effluent	0.74
Paper mill A treated effluent	0.47
Paper mill B treated effluent	1.2
Clay pit	16

The conditioned sewage sludge at two sewage conditioning plants which used polyacrylamide was found to contain acrylamide at levels below the standard (~0.1 μg/l). The effluent emitted from these plants is further diluted by a factor of at least 10:1 prior to discharge into waterways, and hence the acrylamide monomer content resulting from the use of that particular polyacrylamide flocculant is not expected to be a cause for concern in terms of exceeding the drinking water standard.

In summary, only one British study of effluent and ambient monitoring data for acrylamide compounds is available. No United States monitoring data were noted in the available literature.

III. Health and Environmental Effects

A. Environmental Effects

1. Persistence

a. Biological Degradation, Organisms and Products

Relatively little is known about the environmental fate of acrylamide and its derivatives. Cherry and coworkers (1956) have studied the fate of acrylamide in natural water. Acrylamide (10 ppm) was added to filtered river water which had been supplemented with inorganic nutrients - nitrogen and phosphorus - to supply nutrients to the river microorganisms. The water was aerated by bubbling air at a rate of about one bubble per second. COD analysis at various intervals revealed a rapid loss of acrylamide from the water (Figure 9). When the river water was redosed with acrylamide, faster rates of degradation were observed.

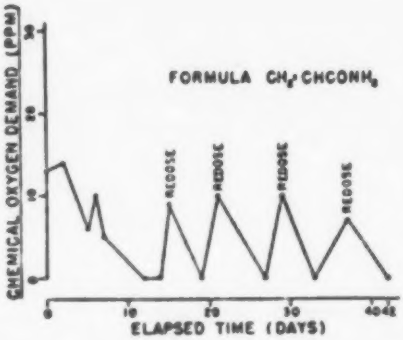


Figure 9. Degradation of Acrylamide in River Water Supplemented with Nitrogen and Phosphorus (1 part P, and 7-10 parts N for each 100 ppm of COD) (Cherry et al., 1956) (Reprinted with permission from Water Pollution Control Federation)

In the river die-away test carried out by Croll and coworkers (1974), river water enriched with 8 ppb of acrylamide was incubated aerobically in a beaker in sunlight. The method of analysis of acrylamide involved bromination of acrylamide to α,β-dibromopropionamide which was extracted and analyzed by electron capture gas chromatography. The authors noted a rapid loss of acrylamide from the river water after a lag period which ranged from 50 - 220 hours. Redosing the river water with acrylamide, or seeding the river water with the microorganisms acclimated to acrylamide, resulted in faster rates of degradation with shorter lag periods (Figure 10). These results suggested that the loss of acrylamide was the result of microbial degradation and that acclimation of the microorganisms prior to degradation was necessary. This was confirmed by Cherry and coworkers (1956), who determined 5-day BOD with 10 ppm of acrylamide using a variety of different seeds. As shown in Table 16, the seed material acclimated to acrylamide yielded a BOD equivalent to about

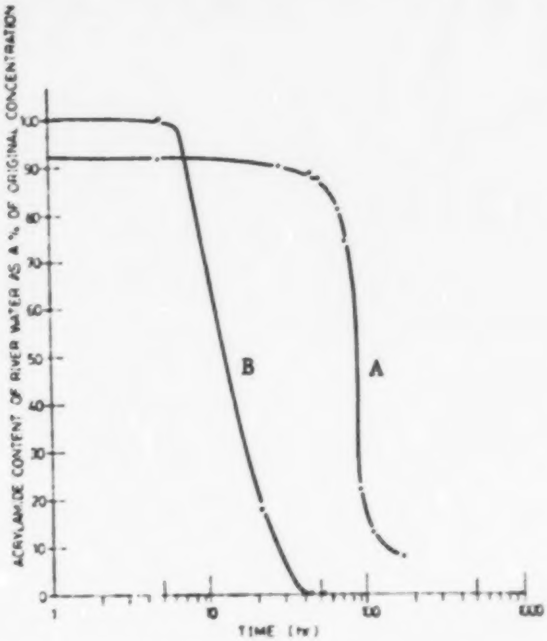


Figure 10. Degradation of Acrylamide in Control and Inoculated Samples of River Water (Croll et al., 1974)
(Reprinted with permission from Pergamon Press Inc.)

A River water
B River water inoculated with acclimated culture

Table 16. Standard 5-Day BOD Test with Acrylamide Using Different Types of Seeds (Cherry *et al.*, 1956)

	Type of Seed	BOD (Expressed as % of COD*)
(i)	River microorganisms acclimated to acrylamide	75
(ii)	River microorganisms acclimated to acrylonitrile	17
(iii)	Sewage seed, unacclimated	13

* COD (ppm) = 1,300,000

75% of COD. On the other hand, when unacclimated seed or seed material which had been acclimated to another substance (acrylonitrile) was used, the BOD was only in the range of 13-17% of COD.

The susceptibility of acrylamide to rapid biological breakdown is also indicated from the studies of Edwards (1975b). In the tanks which he used to expose goldfish to acrylamide, it was found that acrylamide decreased very rapidly if weeds, algae, and microorganisms were present. However, when the tanks were cleaned with permanganate and freed from weeds, the levels of acrylamide remained fairly constant.

Croll and coworkers (1974) investigated the fate of acrylamide under sewage treatment conditions by analyzing the acrylamide levels in the influent and effluent of a sewage works receiving trade effluent containing acrylamide. The authors noted that the works caused a 75% reduction in acrylamide; the levels decreased from 1.1 mg/ℓ to 0.28 mg/ℓ (treatment period unknown). Since acrylamide is very water soluble, significant loss due to adsorption on the sludge seems unlikely. Therefore, the loss may have been largely due to microbial degradation. In an aqueous medium (composition not given) inoculated with

5 mℓ of settled sewage effluent per liter, a breakdown of acrylamide was also observed, but after a lag period. The degradation was more rapid in closed vessels than in open vessels (Table 17), suggesting that anaerobic conditions were preferred for biodegradation.

Table 17. The Degradation of Acrylamide by Sewage Effluent (Croll *et al*., 1974)

Period of experiment (days)	Concentration of acrylamide (mg l^{-1}) Aerated vessels 1	 2	 Closed vessels 1	 2
0	0.06	0.17	0.08	0.16
5	0.06	0.14	0.08	0.15
9	0.08	0.17	n.d.	n.d.
12	0.05	0.08	n.d.	n.d.
16	n.d.	n.d.		

n.d. = Not detected

Although the carbon in acrylamide appears to be utilized fairly rapidly by stream and sewage microorganisms, it is unclear if nitrogen in the molecule can serve as the nitrogen source for growth. Hynes and Pateman (1970) have reported that acrylamide could not serve as the sole nitrogen source for the growth of the fungus *Aspergillus nidulans*. This was attributed to the inability of acrylamide to induce the synthesis of acetamidase, an enzyme involved in amide-N utilization. The conclusion was based on the finding that a regulatory mutant of *A. nidulans*, producing acetamide constitutively, was able to grow on acrylamide as the nitrogen source.

In summary, the available information suggests that acrylamide will biodegrade in the environment. Microorganisms can utilize the carbon in acrylamide for growth, but the fate of nitrogen in the molecule is unclear. The environmental fate of the derivatives of acrylamide has not been studied, and their behavior and fate in the environment is uncertain.

b. Chemical Degradation

Information on the alteration of acrylamide and its derivatives by chemical processes (e.g., hydrolysis, oxidation, photolysis) has been reviewed in Section I-B-2 (p. 16). Unfortunately, no experimental data are available on the nonbiological alteration of acrylamide and its derivatives under environmental conditions.

Acrylamide and its derivatives and polyacrylamide are relatively stable under oxidative conditions at ambient temperatures. Polyacrylamide may be subjected to some hydrolysis in aqueous solution. Some photosensitized polymerization is possible for certain acrylamide derivatives in aqueous solution. Overall, it appears that chemical and photochemical reactions will be of some importance in the environmental fate of acrylamide and its derivatives and polyacrylamide, although any major modification of the molecule as a consequence of these chemical reactions seems unlikely.

2. Environmental Transport

No experimental data are available concerning the environmental transport of acrylamide and its derivatives. Environmental movement of chemicals generally takes place via processes such as adsorption of colloidal substances, volatilization, codistillation, leaching, etc., and is governed by such properties of the compound as solubility in water, volatility, adsorptivity, etc. Acrylamide and most of its derivatives are so water soluble that they will probably be leached through soils and will also migrate through soil and eventually make their way to ground water. In aquatic systems, these compounds will be expected to be contained in the overlaying water, and very little, if any, should reside in the sediment or suspended matter. Therefore, they will be transported with flowing water.

The vapor pressure of a chemical determines to a great extent the possibility of the compound vaporizing into the atmosphere. The low vapor pressure of acrylamide (e.g., 0.007 mm Hg at 25°C) and its derivatives suggests that evaporation should not be appreciable. Chemicals from aquatic systems can be lost by codistillation with water, a phenomenon which is dependent upon the water solubility and vapor pressure of the compound. The high water solubility of acrylamide and its extremely low vapor pressure suggest that appreciable quantities will not be lost to the atmosphere from water. This is supported from the calculated half-life for acrylamide (~ 400 years) in a square meter of water (calculated according to the approach of Mackay and Leinonen, 1975). It should be kept in mind, however, that the equation derived by Mackay and Leinonen (1975) is applicable to low solubility contaminants where water evaporation rate is not appreciably affected by the presence of the contaminant. The equation has been applied with acrylamide even though it is extremely water soluble, only to obtain the order of magnitude of the losses via codistillation.

In summary, although no experimental data on environmental transport of acrylamide and its derivatives are available, on the basis of the physical properties, it can be predicted that these chemicals will have a fairly high mobility in aqueous and soil environments. It is unlikely, however, that they will enter and be distributed through the atmosphere to a significant extent. This conclusion assumes that acrylamide compounds are stable enough in the environment to permit time for transport; the information on biodegradation suggests that this may not be the case.

3. Bioaccumulation and Biomagnification

No experimental data could be found in the literature concerning bioaccumulation and biomagnification potential of acrylamide and its derivatives. Kenaga (1972) has suggested that some of the characteristics of a molecule which will affect its bioaccumulation are solubility, partition coefficient, and polarity. In view of the fact that a large number of the acrylamide compounds are extremely water soluble, it is unlikely that they will bioaccumulate in food chain organisms in significant quantities. Furthermore, in the case of acrylamide, it is expected that it will be fairly rapidly attacked by microorganisms in the environment and, consequently, may not come in contact with food chain organisms at appreciable concentrations.

Metcalf and Lu (1973) have found that the ecological magnification of several chemicals (concentration in organisms/concentration in water) in their model aquatic ecosystem follows a straight line relationship with water solubility. Their data show that for a log of the water solubility (ppb) > 7, the ecological magnification becomes insignificant. For acrylamide and all of its derivatives for which water solubilities are known, the log of the water solubility (ppb) is > 7 (e.g., log H_2O sol. (ppb) is 9.33 and 7.47 for acrylamide and N,N-methylenebisacrylamide, respectively). On the basis of the information summarized above, it can be suggested that acrylamide and its derivatives will not biomagnify in the food chain.

B. Biological Effects

Acrylamide exerts its primary biological effect on the nervous system. Man, other mammals, and certain non-mammalian vertebrates seem to respond in about the same way. In acute intoxication, the central nervous system is most severely affected. The major signs of acute exposure include ataxia, weakness, tremors, and convulsions. In subacute and chronic intoxication, both the central and peripheral nervous systems are affected, with the clinical effects of the peripheral nervous system damage being the most prominent. In such exposures, tremors and convulsions are usually absent. The major features of prolonged intoxication are ataxia and weakness, the latter first appearing distally in the hindlimbs and later extending more proximally. In severe exposures, weakness and paralysis of all four limbs may develop.

The acrylamide derivatives have been much less extensively studied than acrylamide. These compounds appear to be considerably less toxic than acrylamide, and only a few N-substituted acrylamides seem to have chronic toxicological properties similar to those of acrylamide. Little information is available on the acute toxicity of these compounds.

1. Toxicity and Clinical Studies in Man

a. Occupational Studies

Human intoxication from industrial exposure to acrylamide has been recognized for over twenty years (Golz, 1955). Although the last published report of human poisoning appeared in 1972 from France (Cavigneaux and Cabasson, 1972), Spencer and Schaumburg (1974a) indicate that cases are still appearing in the United States.

The general picture of acrylamide intoxication in man is not dissimilar to that seen in laboratory mammals (see Section III-B-2, p. 85).

The common signs of acrylamide poisoning in man are limb fatigue, unsteady walking, general impairment of limbs, skin peeling on the hands, and excessive sweating. In addition, eye irritation, sensory impairment, dizziness, slurred speech, gastrointestinal disturbances, and muscle pain may develop. However, evaluations of cases of industrial intoxication are complicated by the inability to precisely define the degree of exposure. Thus, because many clinically documented cases may involve both acute and chronic exposures, the latency period and nature of the symptoms vary markedly.

Six cases of acrylamide neuropathy have been reported from England (Garland and Patterson, 1967). The common clinical characteristics and some other relevant details from these exposures are summarized in Table 18.

Table 18. Main Signs and Symptoms of Occupational Acrylamide Intoxication in Six Cases in England

(Garland and Patterson, 1967)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age in years	19	23	30	56	59	57
Exposure in weeks	6	12	12	8	60	4
Hands peeling	X	X		X		
Increased sweating of feet and hands	X	X		X	X	
Fatigue, lethargy, and drowsiness	X		X	X	X	X
Muscle weakness	X	X	X	X	X	X
Muscle pain	X					X
Abnormal skin sensations		X		X	X	X
Sensory loss	X	X	X	X	X	X
Absent reflexes	X	X	X	X	X	X
Romberg's sign positive	X	X	X	X	X	X

In that no cases of acrylamide intoxication were found in factories where dermal contact was minimized, Garland and Patterson (1967) state that excessive dermal contact rather than inhalation was the major route of exposure in these cases. Muscular weakness and loss of reflexes are common to all of these exposures and are also typical of subacute mammalian intoxication. Some degree of sensory impairment is also common to all of the above occupational intoxications. In Case 4, sensory loss was so severe that the individual felt no pain when his fingers were being burnt by a cigarette. Such severe sensory loss is uncommon even in severe intoxication of other mammals, although sensory nerve damage has been demonstrated in pathological and electrophysiological findings. In Case 1, severe ataxia appeared without marked sensory impairment.

Cases 1, 4, and 6 also show signs of central nervous system (CNS) effects common in acute mammalian intoxication. In Case 6, CNS involvement is suggested by the presence of truncal ataxia. Case 1 had general body tremors which are also associated primarily with acute intoxication. Both Cases 1 and 4 exhibited slurring of speech, which might be indicative of midbrain or cranial nerve damage. [As detailed in Section III-B-2-c, p. 78, the midbrain may be a primary target of acrylamide in the acute poisoning of mammals.] However, Case 4, which had both severe sensory loss and signs of acute intoxication, also developed urinary incontinence during recovery similar to that seen in chronically exposed mammals.

Because of the appearance of both peripheral and central nervous system effects described above, Garland and Patterson (1967) postulated that acrylamide caused both peripheral neuropathy and midbrain lesions in man. In Japan, Fujita and coworkers (1960) proposed a similar dual effect based on the symptoms found in ten cases of industrial exposure to acrylamide. More recently, to sympathetic overactivity. Contact was discontinued by hospitalization after 14 weeks. Apparently, full recovery occurred after an additional 14 weeks.

The six cases described from France (Cavigneaux and Cabasson, 1972; Graveleau et al., 1970; Morviller, 1969) also present no remarkable characteristics. Cavigneaux and Cabasson (1972) emphasize that skin lesions do not always serve as an early warning of acrylamide exposure. This is evident in the report of Auld and Bedwell (1967), as well as in results shown in Tables 18 and 19. Morviller (1969) indicated that acrylonitrile rather than acrylamide might be the neuropathic agent in four cases where exposure to both chemicals occurred. However, Barnes (1970) has indicated that acrylonitrile is not neurotoxic to rats (see Section III-B-2-d-iv, p. 111).

In all cases in which details are available, the neuropathic effects of acrylamide in man are reversible when contact is discontinued. However, one individual who developed severe acrylamide neuropathy displayed imperfect recovery with evidence of spastic ataxia and sensory loss suggestive of damage to long ascending and descending spinal cord tracts (Schaumburg and Spencer, 1976).

b. Neurophysiology and Pathology of Occupational Exposures

Both Fullerton (1969) and Takahashi and coworkers (1971) have described functional and structural changes in humans after occupational intoxication with acrylamide. Fullerton (1969) examined three of the cases described by Garland and Patterson (1967) [cases 1, 4, and 5 - see Table 18]. Both pathological and electrophysiological measurements conformed to detailed data on acrylamide neuropathy in experimental mammals. Electrophysiological measurements indicated that the distal portions of the nerves were more severely affected than proximal portions and sensory fibers were more severely affected than motor fibers. Fiber diameter distribution measurements indicated that large diameter fibers are most susceptible to acrylamide intoxication (see Figure 11).

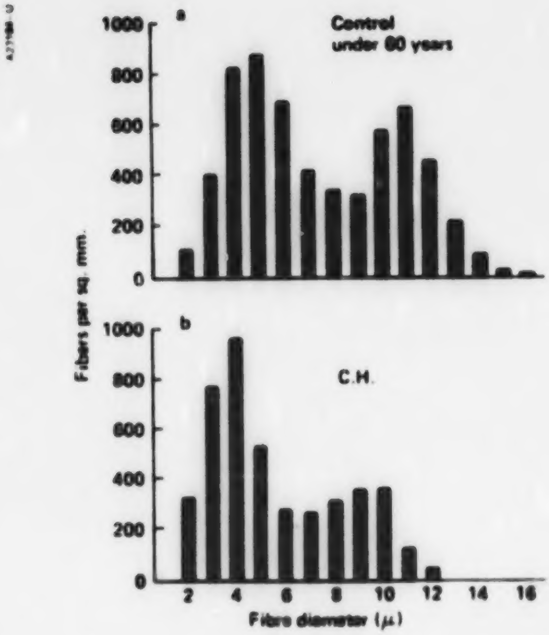


Figure 11. Histogram of Fiber Diameter. a=control histogram for eight sural nerves calculated from data of O'Sullivan and Swallow (1968); b=acrylamide patient C.H.

Nearly identical patterns of nerve fiber damage have been noted in baboons (Hopkins, 1970 - see Figure 16, p. 106). A general decrease in internodal length relative to fiber diameter indicated that regeneration was occurring (see p. 107). A marked dispersion of muscle response to nerve stimulation further indicated a "dying back" neuropathy typical of chronic acrylamide exposure in other mammals. Little effect was seen on nerve conduction velocity, although decreased conduction velocity is common in severely intoxicated mammals (Fullerton, 1969 and 1970).

Similar results have been noted by Takahashi and coworkers (1971). While nerve conduction velocity remained normal in most patients, action potentials of both median and tibial nerves were greatly reduced. In addition, three of the fifteen patients had abnormal electroencephalograph (EEG) recordings indicative of central nervous system involvement.

c. Other Human Studies

Igisu and coworkers (1975) have described five cases of central and peripheral nervous system intoxication which occurred in a family using water from a well contaminated with 400 ppm acrylamide. All five individuals developed signs of neurological disturbance within one week after acrylamide had been used in chemical grouting at a site 2.5 meters from the family well. Early signs of intoxication were characteristic of CNS damage and included severe truncal ataxia, mental confusion, and hallucinations. After exposure was terminated, CNS effects markedly diminished within about one week. However, after or during CNS recovery, signs of peripheral nervous system intoxication - numbness of the limbs, absence of ankle jerks, or reduction of sensory conduction velocity of the sural nerve - developed in three individuals. By four months after exposure, all individuals appeared normal. Acrylamide derivatives have not been cited in published cases of human intoxication.

2. Effects on Non-Human Mammals

a. Absorption, Distribution, and Elimination

No information is available on the absorption kinetics of acrylamide or acrylamide analogues. In that acrylamide is toxic to rats, mice, dogs, cats, and guinea pigs by oral, dermal, or inhalational exposures (Hamblin, 1956; see also Section III-B-2-c, p. 78 and d, p. 85), absorption by these routes may be presumed (Anon., 1969; Auld and Bedwell, 1967). Fassett (1963) states that N,N-dimethylacrylamide, but not N-isopropylacrylamide, is readily absorbed through the skin by guinea pigs. However, this statement is based on observations of toxicological responses and not on actual monitoring of acrylamide absorption.

Once in the blood stream, levels of free acrylamide and free N-methylolacrylamide decrease rapidly. This is illustrated in Figure 12,

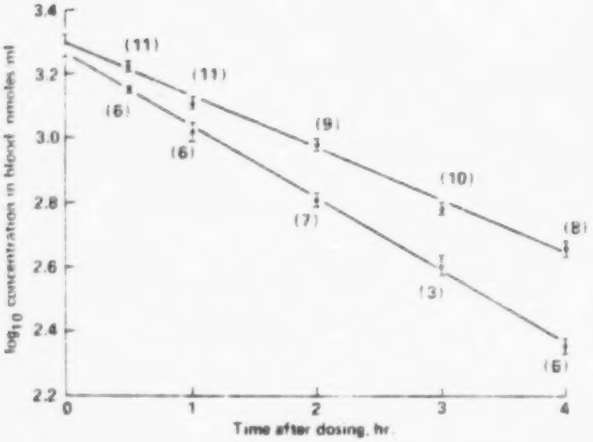


Figure 12. Blood Concentrations of Acrylamide (●) and N-Methylolacrylamide (o) After Intravenous Injections to Rats (Edwards, 1975a) In this figure, the bars represent standard errors and the number of rats is given in parentheses.

which gives blood levels of free acrylamide and free N-methylolacrylamide in rats after intravenous injections of 100 mg/kg acrylamide and 140 mg/kg N-methylolacrylamide. The calculated blood half-lives for free acrylamide and N-methylolacrylamide are 1.90 and 1.55 hours, respectively. By extrapolating these curves back to zero time, dilution volumes approximate that of total body water for both compounds in the unbound form.

Twenty-four hours after identical doses to rats, Hashimoto and Aldridge (1970) demonstrated that most of the label from [1-^{14}C] acrylamide and [1-^{14}C] methylolacrylamide is protein bound (see Table 20). Although the labeled material was not identified, the available information summarized in the following section suggests that extensive metabolism of these compounds to carbon dioxide does not occur. Consequently, the distribution of labeled material probably represents the parent compounds or slightly modified metabolites.

The patterns of binding and tissue distribution are similar for both acrylamide and N-methylolacrylamide. Going from one to four days after dosing, levels in all tissue except blood decline. During all periods measured, blood contains the highest levels of labeled material, primarily bound to protein. The increase of label in blood during the first four days after dosing suggests that both of these compounds have a high affinity for blood cells. In vitro studies consistent with this interpretation are summarized in Section III-B-7-b (p. 124). After blood, the next highest levels of both compounds are found in the liver and kidney. No extremely high affinity is apparent in nerve tissue. However, Ando and Hashimoto (1972) have shown that the distal half of the sciatic nerve accumulates 2.4 times as much ^{14}C-acrylamide as the proximal half and four times as much as the brain. This distribution could be a factor in the more severe pathological changes usually noted in the distal portions of nerve fiber in acrylamide intoxication (see Section III-B-2-d-ii, p. 103).

Table 20. Distribution of [^{14}C] in Tissues of Rats After Single Intravenous Injections of [1-^{14}C] Acrylamide and [1-^{14}C] N-Methylolacrylamide

(Hashimoto and Aldridge, 1970)

Time After Administration	Tissue	Homogenate	"Free and Soluble" (nmoles/g original tissue)	Protein Bound
Acrylamide (100 mg/kg body wt)				
	Blood	1280	160	938
	Plasma	63	0.0	—
	Brain	262	105	156
24 hours	Spinal Cord	175	44	110
	Sciat. N.	149	60	—
	Liver	368	70	323
	Kidney	508	195	280
	Blood	1360	7.4	920
	Plasma	26	0.0	—
	Brain	151	20	95
4 days	Spinal Cord	131	19	89
	Sciat. N.	100	16	89
	Liver	142	20	158
	Kidney	248	66	161
	Blood	772	1.8	920
	Plasma	6.0	0.0	—
	Brain	72	3.3	49
14 days	Spinal Cord	71	2.8	44
	Sciat. N.	57	0.0	—
	Liver	57	1.6	61
	Kidney	91	1.2	76
N-methylolacrylamide (140 mg/kg body wt)				
	Blood	1200	73	1130
	Plasma	35	0.0	26
	Brain	157	39	104
24 hours	Spinal Cord	109	25	69
	Sciat. N.	101	0.0	93
	Liver	262	2.7	266
	Kidney	266	75	214
	Blood	1370	0.0	1220
	Plasma	13	0.0	13
	Brain	95	0.0	79
4 days	Spinal Cord	70	0.0	64
	Sciat. N.	62	0.0	46
	Liver	[illegible]	0.0	146
	Kidney	[illegible]	2.1	165

Each value is the mean from three experiments. The "free and soluble bound" is that remaining in solution after treatment with 5% trichloroacetic acid

In addition to general tissue binding, Hashimoto and Aldridge (1970) have also demonstrated that small amounts of label appear in the DNA and RNA fractions of rat brain and liver twenty-four hours after intravenous administration of 100 mg/kg of acrylamide (see Table 21). However, because the nucleic acid fractions were not pure, the significance of this low level of activity is questionable. Based on the data in Table 20, 0.5-2.0% protein contamination could account for the observed activity. Although the investigators did not specify the levels of protein contamination, they state that the observed activity indicates "an extremely low level of incorporation."

Table 21. [^{14}C] in Nucleic Acids Isolated from Rat Brain and Liver After a Single Dose of [1-^{14}C] Acrylamide to Rats (Hashimoto and Aldridge, 1970)

		nmoles/mg
Brain	RNA	0.0075
	DNA	0.018
Liver	RNA	0.023
	DNA	0.016

The elimination of acrylamide after a single intravenous injection (100 mg/kg) is initially rapid. As indicated in Figure 13, urinary elimination is predominant with 40% excreted after one day, 60% after three days, but very little additional urinary elimination between three and sixteen days after dosing. The urinary metabolites were not identified. Expiration of labeled CO_2 accounts for only about 6% of the total dose, with most appearing after the first eight hours. Spencer and Schaumburg (1974a) have summarized unpublished reports indicating that rats excrete 40-65% of labeled acrylamide after one day and 60-85% after 3-4 days. However, based on the information in Figure 13, approximately 30% of the original dose is not excreted by rats by two weeks after dosing (Hashimoto and Aldridge, 1970).

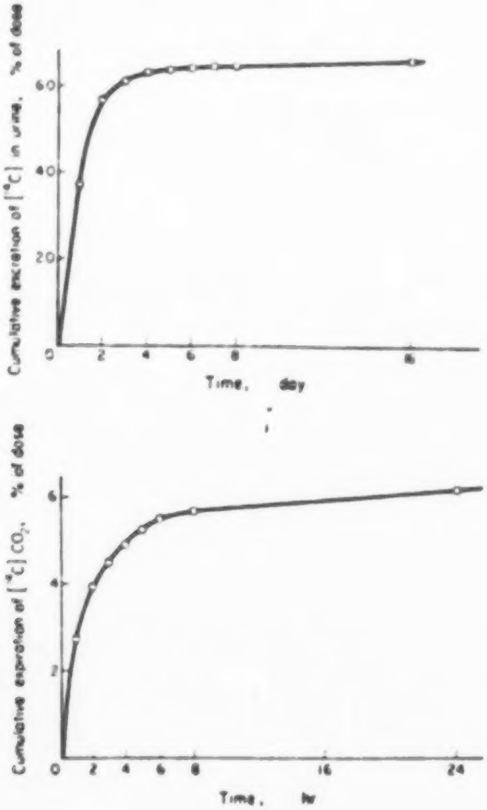


Figure 13. Excretion of [^{14}C] in Urine and Expiration of $^{14}CO_2$ After a Single Dose of [1-^{14}C] Acrylamide. 100 mg/kg (7.3 μc) was administered intravenously. The results are the means of the results for two rats. (Hashimoto and Aldridge, 1970) (Reprinted with permission from Pergamon Press Inc.)

b. Metabolism

The metabolism of acrylamide has not been extensively investigated. The presence of $^{14}CO_2$ after injections of [1-^{14}C] acrylamide, accounting for 6% of the total dose after eight hours, clearly indicates that an enzymatic apparatus for the degradation of acrylamide is present in rats (see Figure 13, p. 74; Hashimoto and Aldridge, 1970). The rapid decrease in such degradation after eight hours may be due to extensive binding of acrylamide to various tissue components.

As indicated above, the nature of acrylamide urinary metabolites has not been determined. However, Edwards (1975a) has demonstrated that both acrylamide and N-methylolacrylamide are conjugated with glutathione prior to biliary elimination. Two to four hours after intraperitoneal injections of acrylamide (100 mg/kg) or N-methylolacrylamide to rats, liver glutathione levels are lowered to 36% of normal and remain depressed for twenty-four hours. Similarly, Hashimoto and Aldridge (1970) have shown that acrylamide and N-methylolacrylamide decrease levels of nonprotein sulfhydryls in the brain, spinal cord, and liver of rats. Thus, glutathione conjugation of acrylamide may be a detoxication reaction in nervous tissue. The reactivity of acrylamide and its analogues with glutathione and other sulfhydryls is discussed in Section III-B-7-e (p. 124).

Because acrylamide analogs are apparently much less toxic than acrylamide itself, the conversion of these analogs to acrylamide is a potentially important metabolic reaction. However, Edwards (1974, 1975a) has found little indication that such reactions occur to a significant extent. Less than 9% of N-methylolacrylamide is converted to acrylamide in rats. No evidence was found indicating that either N-methylacrylamide or N,N-diethylacrylamide is converted to acrylamide (Edwards, 1974, 1975a).

The mechanism for the predominant neurological effects of acrylamide and various acrylamide analogues has not been determined. No enzymes have been identified as targets of acrylamide activity. Oral doses of 0.3 - 3 mg/kg/day over a one year period do not affect blood cholinesterase activity in cats (McCollister *et al.*, 1964). Acrylamide given orally to rats at 400 ppm for 20 days has no effect on oxygen consumption of brain slices (Hashimoto and Aldridge, 1970). As indicated in Section III-B-7 (p. 123), acrylamide does not seem to interfere with mitochondrial activities including oxidative phosphorylation. However, acrylamide has been shown to alter patterns of amino acid and nucleic acid incorporation and may affect the axonal flow of proteins.

The effect of acrylamide on amino acid incorporation into nervous tissue has been studied by Hashimoto and Ando (1973) and Asbury and co-workers (1973). Rats fed acrylamide at 500 ppm for four weeks evidenced altered incorporation patterns of both ^{14}C-lysine and ^{35}S-methionine in spinal cord and sciatic nerve tissue but not in brain cortex or liver (see Figure 14 for lysine patterns).

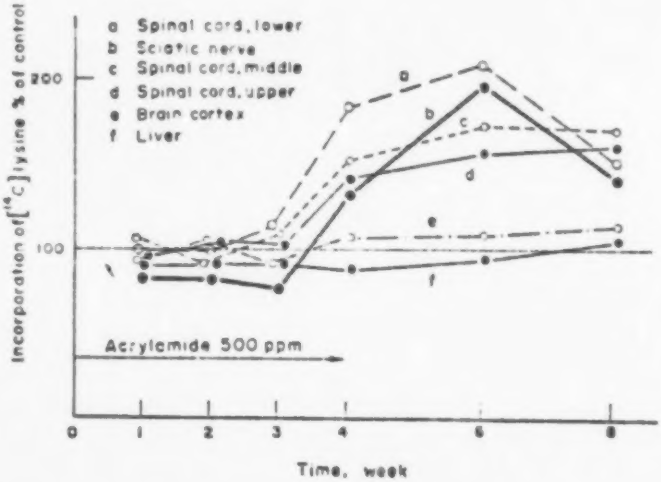


Figure 14 [^{14}C]Lysine Incorporation Into Tissue Proteins of Rats Dosed with Acrylamide for 4 Weeks Expressed as Per Cent of Controls at Various Times (Hashimoto and Ando, 1973) (Reprinted with permission from Pergamon Press Inc.)

In spinal cord tissue, both lysine and methionine incorporation remained normal during the first three weeks of exposure. Between four and six weeks after initial exposure, incorporation of both amino acids increased to nearly 100% above normal, but by the eigth week (fourth week of recovery), the incorporation had a tendency to return to normal. The lower portions of the spinal cord showed the greater increase for both amino acids. In the sciatic nerve, methionine incorporation followed the same pattern, remaining normal for the first three weeks and then increasing by about 80% in the sixth week. The pattern for lysine was similar except that incorporation during the first three weeks of exposure was depressed to about 80% of control levels (see Figure 14). Autoradiographic studies indicated that increased lysine incorporation occurred primarily in the anterior horn cells of the spinal cord and the Schwann cells of the sciatic nerve. Clinically, mild signs of intoxication (hind limb weakness) appeared after two weeks, paralysis after four weeks, and recovery from paralysis by five to six weeks. Consequently, the above patterns of amino acid incorporation were attributed to regeneration of damaged nerve tissue (Hashimoto and Ando, 1973). In mice given 250 ppm in water, Asbury and coworkers (1973) noted a 40% decrease in the incorporation of H^3-leucine into the perikarya of the anterior horn cells of the lumbar spinal cord. This decrease initially occurred seven days after the beginning of exposure, preceding the onset of clinical and pathological signs by one week. No attempt was made to monitor amino acid incorporation during recovery.

Increased nucleic acid incorporation has also been noted in the sciatic nerve of animals during acrylamide intoxication. In mice given acrylamide at 250 ppm for 45 days, increased ^{3}H-thymidine incorporation into the Schwann cells along the sciatic nerve coincided with the onset of clinical symptoms after about 23 days. Labeling peaked after 30 days and fell rapidly after acrylamide exposure was terminated. The labeling patterns observed correlated better with the duration of acrylamide exposure than with the degree of histological damage. In rats given acrylamide orally for two weeks [dose not specified], an increase in ^{3}H-uridine was also noted along the sciatic nerve (Ando and Hashimoto, 1971).

An impairment of anterograde axonal transport of materials (axonal flow) has been suggested as a possible mechanism for the neuropathic effects of acrylamide. Pleasure and coworkers (Pleasure _et al._, 1969; Pleasure and Engel, 1970) used the movement of ^{3}H-leucine along the axons to measure slow axonal flow (1-2 mm/day). In most cats showing clinical signs of acrylamide intoxication after daily doses of 20 mg/kg, axonal flow in both the dorsal (sensory) and ventral (motor) root ganglia was greatly suppressed. Consistent with toxicological data (see Section III-B-2-d, p. 105), sensory flow seemed somewhat more affected than motor flow. However, in two cats with acrylamide intoxication, no depression of axonal flow was seen. Bradley and Williams (1973) measured both slow and fast (several hundred mm/day) axonal flow in acrylamide-intoxicated cats and found no evidence of diminished slow waves. The crest but not the fronts of fast waves was reduced. Because the degree of histological damage did not correspond to the magnitude of flow reduction, Bradley and Williams (1973) concluded that impairment of axonal flow is not a major factor in the development of acrylamide neuropathy.

c. Acute Toxicity

(i) Acrylamide

Studies on the acute toxicity of acrylamide to various mammals are summarized in Table 22. McCollister and coworkers (1964) have estimated

Table 22. Acute Toxicity of Acrylamide to Various Mammals (Single dose unless otherwise specified; See text for details)

Animal	Route	Dose (mg/kg)	Response	Reference
Mice, male albino	oral	170 (130-220)	LD_{50}, many delayed deaths	Hamblin, 1956
Rats, female, Porton str., 8 weeks	oral	100 203 (166-249)	Fine tremors, no deaths LD_{50} [illegible], death in [illegible] days	Fullerton and Barnes, 1966
Rats	oral	200	LD_{50}	[illegible], 1969
Rats, Porton str., young adult	oral	200*	Lethal within a few days	Barnes, 1970
Rats, female, young adult	oral	126 252	No lethality in five animals tested 1/5 died after one day	McCollister et al., 1964
Rats	i.p.	120	LD_{50}, death usually in 1-2 days	Druckrey et al., 1953
Guinea pigs, male	oral	126 252	No lethality in four animals tested 4/4 died overnight	McCollister et al., 1964
Rabbits, male and female	oral	63 126 252	No deaths in four animals tested 1/4 died 4/4 died overnight	McCollister et al., 1964
	dermal	63, 126, and 500 1000	Not fatal Fatal in 2 days (one animal tested)	
Cats	i.p.	100** 75-1000	Ataxia Severe C.N.S. effects	Kuperman, 1958
Cats	i.p.	100	Convulsions after 24 hours No deaths Complete recovery	Spencer and Schaumburg, 1974b
Cats	i.v.	100	Severe neurotoxic effects after 24 hours No deaths	McCollister et al., 1964
Monkeys	i.p.	200* 200***	Lethal one day after last injection Lethal	McCollister et al., 1964

* 100 mg/kg/day x 2 consecutive days

** 50 mg/kg/day x 2 consecutive days

*** 50 mg/kg/day x 4 consecutive days

the oral LD_{50} for rats, guinea pigs, and rabbits at 150-180 mg/kg. This estimate is similar to the observed oral LD_{50}'s for rats (203 mg/kg; Fullerton and Barnes, 1966) and mice (170 mg/kg; Hamblin, 1956). Although information on other routes of exposure for these mammals is sparse, the intraperitoneal LD_{50} of 120 mg/kg for rats (Druckrey et al., 1953) indicates that this route may be somewhat more toxic than oral administration. Conversely, dermal exposure was fatal to a rabbit at about four times the oral lethal dose (McCollister et al., 1964). While LD_{50} estimates are not available for cats or monkeys, the data summarized in Table 22 suggest a lethal range similar to that of the other mammals tested. In most fatal exposures, death occurs 1-3 days after dosing. Hamblin (1956) states that mice experienced delayed death but does not specify the period of delay.

The signs of acrylamide intoxication show marked similarity. At oral doses below the lethal range, neurotoxicity is relatively mild. Fullerton and Barnes (1966) noted only fine tremors in rats at 100 mg/kg. At 126 mg/kg, McCollister and coworkers (1964) noted lethargy, a slight weight loss, but no tremors in rats; only a very slight weight loss in guinea pigs; and tremors as well as pupil dilation in rabbits. Cats given intraperitoneal injections of 50 mg/kg/day for 2 days exhibited both tremors and ataxia (Kuperman, 1958). Sussman et al. (unpublished) noted loss of functional activity of mesenteric pacinian corpuscles, a type of peripheral sensory receptor, after 1-2 days in cats receiving only 10-20 mg/kg of acrylamide subcutaneously.

At higher doses approximating the LD_{50}, the primary signs of acrylamide intoxication are characteristic of central nervous system stimulation. Kuperman (1958) outlines the general sequence of responses in cats given intraperitoneal injections of acrylamide at 75-1000 mg/kg: ataxia, tremors, weakness, vomiting, defecation, mass sympathetic stimulation, behavioral changes suggestive of hallucinations, and periodic clonic-tonic convulsions prior to death.

Ataxia, labored respiration, and convulsions have also been noted in fatally exposed mice (Hamblin, 1956) and rats (Druckrey *et al.*, 1953). In addition, Druckrey and coworkers (1953) noted behavioral changes in rats which were described as resembling fright or excitement. A rather atypical response has been observed in one monkey given intraperitoneal injections of 100 mg/kg acrylamide on two successive days. Prior to death, at one day after the last injection, the animal had no sense of balance but was able to use its muscles for crawling. No convulsions were noted (McCollister *et al.*, 1964). The direct cause of death, at least in the lower mammals, has been attributed to respiratory failure associated with laryngeal spasm and obstruction (Riker, 1954) or acute pulmonary obstruction (Druckrey *et al.*, 1953).

The time course of acute acrylamide exposure is characterized by a minimum latent period between dosing and the onset of adverse effects as well as apparent complete recovery in animals surviving even severe intoxication. Kuperman (1958) noted an inverse relationship between the magnitude of the dose and the length of the latent period. In cats given intravenous injections of acrylamide, the doses and respective latent periods were as follows: 75 mg/kg, 7-12 hours; 1000 mg/kg, 1 hour; and 5,000 mg/kg, 15 minutes. Recovery from acrylamide intoxication has been described by several investigators. Rats which survive doses near the LD_{50} show fine tremors but recover completely after about two days (Fullerton and Barnes, 1966). Hamblin (1956), while not specifying the period to complete recovery, notes that rats surviving doses above the LD_{50} experienced peripheral motor weakness. A cat receiving a single intraperitoneal injection of 100 mg/kg acrylamide exhibited severe symptoms after 24 hours but survived, having only slight unstableness after two weeks (McCollister *et al.*, 1964). At the same dose [route not specified], Spencer and Schaumburg (1974b) report that cats recover completely two days after dosing.

The histopathological effects of acrylamide poisoning in a monkey receiving intraperitoneal injections of 100 mg/kg on two consecutive days included congestion of the lungs, congestion of the kidneys with degeneration of the convoluted tubular epithelium and glomeruli, as well as necrosis and fatty degeneration of the liver. The brain and spinal cord of cats receiving 100 mg/kg acrylamide intraperitoneally were normal (McCollister et al., 1964). Similarly, in rats receiving doses of acrylamide near the LD_{50}, no macroscopic lesions were found in the peripheral nerves, although fine fatty infiltration of the liver was noted. This latter effect is not seen in chronic poisoning (Fullerton and Barnes, 1966). Druckrey and coworkers (1953) note that fatal acrylamide intoxication resulted in abnormally rapid carcass rigidity which persisted for about as long as normal rigor mortis.

The mechanism of acute acrylamide intoxication has received relatively little attention. Kuperman (1958) has performed various surgical procedures on the central nervous system of cats in an attempt to define acrylamide's site of action. Doses of 500 mg/kg to decerebellate and decorticate cats induced ataxia, tremors, sympathetic nervous system stimulation, and convulsions typical of the response of surgically unaltered cats. Supracollicular decerebrate cats (brain stem intact), at doses of 400-700 mg/kg acrylamide, also experienced moderate convulsions but no signs of sympathetic stimulation. At the same dose levels, infracollicular decerebrate cats (brain stem transected) showed only brief periods of abrupt muscular contraction (myoclonus). Spinal (T-12 or L-1) cats, at doses of 500 mg/kg acrylamide, evidenced only spasmodic movements of the knee (patellar clonus). Electroencephalographs of intact cats revealed that acrylamide-induced convulsions were associated with sustained high-voltage and hypersynchronous electrocortical activity. Generally, EEG seizure patterns in decerebrate cats were less prolonged and lacked high-voltage hypersynchrony. Thus, typical acrylamide convulsions and severe EEG seizures require an intact brain stem (Kuperman, 1958).

Apart from its neurotoxic effects, acrylamide has been tested for both skin and eye irritation. A 10% aqueous solution applied repeatedly to rabbits elicited no response in intact skin, and only transient erythema and edema in abraded skin. A 10% aqueous solution applied to the eyes of rabbits produced slight pain and conjunctival irritation, with complete recovery after 24 hours. A 40% solution applied to the eye without washing produced conjunctival irritation and significant corneal injury. Complete recovery from corneal damage occurred after 24 hours, while conjunctival damage healed slowly (McCollister et al., 1964).

(ii) Substituted Acrylamides

All of the acrylamides thus far examined are less toxic in acute exposures than acrylamide itself. Table 23 summarizes the available information on the acute toxicity of substituted acrylamides. For the most part, these studies were conducted to approximate dose levels for subacute or chronic neurotoxicity, and thus, few details are available on the acute responses. Lethal doses of both methacrylamide and N-methylolmethacrylamide cause damage to the central nervous system of rats, rabbits, and mice (Strizhak, 1967). In addition, methacrylamide applied to rabbit skin - 1 g moist solid over 12 sq. cm. for 4 hours - resulted in minor primary irritation (Rohm and Haas, 1955). Oral doses of N,N-dimethylacrylamide caused secretions around the mouth and eyes as well as convulsions

Table 23. Acute Toxicity of Substituted Acrylamides

Chemical	Organism	Route	LD_{50}(mg/kg)	Reference
Methacrylamide	Rat	Oral	1,223	Strizhak, 1967
	Rabbits	Oral	1,865	
	Mice	Oral	475	
N-Methylolmethacrylamide	Rat	Oral	312	Strizhak, 1967
	Rabbit	Oral	328	
	Mice	Oral	400	
N-Methylolacrylamide	Rats	i.p.*	563 (±20)***	Hashimoto and Aldridge, 1970
	Mice	Oral	420	American Cyanamid Co., 1968
N,N-Dimethylacrylamide	Rat	Oral	200-400	Fassett, 1963
	Mice, male	Oral	485	Hayashi _et al_., 1974
	Mice, female	Oral	460	
	Mice, male	s.c.**	580	
	Mice, female	s.c.	590	
N-Isopropylacrylamide	Rat	Oral	350	Fassett, 1963
N-_t_-Butylacrylamide	Rat	Oral	1,950	American Cyanamid Co., 1954
N-t-Octylacrylamide	Rat	Oral	1,020	American Cyanamid Co., 1958
N,N'-Methylenebis-acrylamide	Rat	Oral	390	American Cyanamid Co., 1954
Diacetone acrylamide	Rat	Oral	2,000-5,000	Lubrizol Corp., no date, a
	Rodents	n.s.	7,000	Lubrizol Corp., no date, b

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* Intraperitoneal injection

** Subcutaneous injection

*** $LD_{50} \pm 1.96$ standard deviation in rats. Dermal applications of 0.5 mℓ/kg were lethal to guinea pigs. Diacetone acrylamide is also reported to be nonirritating to the eyes and skin (experimental animal not specified) (Lubrizol Corp., no date a, b). Further details on the acute toxicity of these compounds are not available.

Based on the rather limited data presented in Table 23, no clear pattern is evident in the acute toxicity of the substituted acrylamides. α-Methyl substitution of acrylamide to form methacrylamide results in markedly decreased toxicity. As in oral acrylamide exposures, mice seem more susceptible than rats to methacrylamide, with the difference in susceptibility apparently enhanced by the α-methyl group. However, α-methyl substitution seems to have no apparent effect on the acute toxicity of N-methylolacrylamide as compared to N-methylolmethacrylamide. While most of the N-substituted acrylamides are far less toxic than acrylamide, N,N'-methylenebisacrylamide is about equitoxic with acrylamide on a molar basis. In that N,N'-methylenebisacrylamide does not cause peripheral neuropathy on chronic exposure (see Section III-B-2-d-iv, p. 116), its high toxicity relative to other N-alkyl acrylamides is probably not attributable to metabolic acrylamide formation.

d. Subacute and Chronic Toxicity

Unlike acute exposures which primarily affect the central nervous system, repeated exposures to acrylamide and a few acrylamide derivatives damage the peripheral as well as the central nervous system. While the nature of peripheral nerve damage has been well characterized, the full extent and locus of central nervous system damage are unclear. Typically, neurotoxic exposures initially cause bilateral weakness, which appears first in the hind limbs and may progress to the fore limbs. In more severe exposures, the clinical picture may include ataxia, paralysis of all four limbs, and other signs of neurological disturbance, as well as secondary toxic effects such as weight loss. These clinical signs are accompanied by concurrent degeneration of vulnerable peripheral and central nerve fiber pathways. Degeneration characteristically commences in the distal regions and slowly ascends the affected nerve fibers, sparing the nerve cell bodies. Consequently, this pathological process is often referred to as the "dying-back process" or "dying-back polyneuropathy" (Cavanagh, 1964). Spencer and Schaumburg (1976, 1977) use the term "central-peripheral distal axonopathy" to emphasize the concurrent central and peripheral nervous system damage to the distal axons in chronic acrylamide intoxication. Electrophysiologically, decreased neural conduction velocity and amplitude also accompany gross signs of acrylamide neurotoxicity. Acrylamide neuropathy has recently been reviewed by Spencer and Schaumburg (1974a and b, 1975).

Along with acrylamide, other chemicals which produce similar peripheral neurological disturbances and central-peripheral distal axonopathy include: triorthocresyl phosphate, some alkyl phosphates, lead, arsenic, methyl mercury salts, thallium, certain organophosphates, isoniazid, nitrofurantoin, trichloroethylene, tetrachloroethane, methyl n-butyl ketone, and 2,5-hexanedione (Cavanagh, 1964, 1973; McLeod, 1971; Thomas, 1970; Barnes, 1969a and b; Spencer and Schaumburg, 1976). In addition, peripheral neuropathies are also associated with hypoglycemia, uremia, porphyria, deficiencies of either vitamin B_{12} or thiamine, and rheumatoid arthritis (McLeod, 1971; Dyck et al., 1975).

(i) Acrylamide - Gross Toxic Effects and Dose-Response Relationships

General Characteristics

Repeated doses of acrylamide have been shown to induce neurotoxic signs in mice, rats, guinea pigs, cats, dogs, baboons, and monkeys. Some acrylamide exposures producing early signs of acrylamide neuropathy in rats, cats, dogs, baboons, and monkeys are summarized in Table 24. Only continuous

Table 24. Acrylamide Doses Producing Early Signs of Peripheral Neuropathy in Various Mammals

Organism	Route	Dose, Schedule	Days to Initial Effect (Number of Doses)	Cumulative Dose (mg/kg)	Reference
RATS (adult)	Oral	100 mg/kg, 2 doses/week[#]	21(6)	600	Fullerton and Barnes, 1966
		100 mg/kg, 1 dose/week	42(6)	600	
		100 mg/kg, 1 dose/2 weeks	210(15)	1500	″
	i.p.	75 mg/kg, 1 dose/day[x]	4.6	345	Kaplan and Murphy, 1972
	i.p.	50 mg/kg, 3 doses/week	~18(7-8)	350-400	Suzuki and Pfaff, 1973
	i.p.	50 mg/kg, 1 dose/day[x]	6.4	320	Kaplan and Murphy, 1972
	Oral	40 mg/kg/day[*]	14	560	McCollister *et al.*, 1964
	i.p.	40 mg/kg, 1 dose/day[x]	6.7	268	Kaplan *et al.*, 1973
	Oral	30 mg/kg/day[*]	21	630	McCollister *et al.*, 1964
	i.p.	30 mg/kg, 1 dose/day[x]	10.7	321	Kaplan *et al.*, 1973
	Oral	25 mg/kg, 5 doses/week	28(20)	500	Fullerton and Barnes, 1966
	i.p.	25 mg/kg, 1 dose/day[x]	16.8	420	Kaplan and Murphy, 1972
	Oral	9 mg/kg/day[*]	56[+]	504	McCollister *et al.*, 1964
CATS	i.p.	50 mg/kg, 1 dose/day	2(2)	100	Kuperman, 1958
	Oral	20 mg/kg, 1 dose/day	14-21	280-420	Leswing and Ribelin, 1969
	i.p.	20 mg/kg, 1 dose/day	5	100	Schaumburg *et al.*, 1974
	i.p.	10 mg/kg, 1 dose/day	13-16	130-160	Schaumburg *et al.*, 1974
	s.c.	10 mg/kg, 1 dose/day	17-22	170-220	Prineas, 1969
	Oral in chow	3 mg/kg, 5 doses/week	68	144	McCollister *et al.*, 1964
	Oral in water	3 mg/kg, 1 dose/day	70+163	210+489	Schaumburg *et al.*, 1974
	i.v.	1 mg/kg, 5 doses/week	~180	~130	Hamblin, 1956
DOGS	Oral	15 mg/kg, 1 dose/day	21[#]	315	Thomann *et al.*, 1974
	Oral	10 mg/kg, 1 dose/day	28-35[#]	280-350	Hamblin, 1956
	Oral	5 mg/kg, 1 dose/day	21[#]	105	Thomann *et al.*, 1974
PRIMATES	Oral in fruit	20 mg/kg, 1 dose/day	16	320	Hopkins, 1970
	Oral in fruit	15 mg/kg, 1 dose/day	42	630	Hopkins, 1970
	Oral in fruit	10 mg/kg, 1 dose/day	56-97	560-970	Hopkins, 1970
	Oral in water	10 mg/kg, 49 doses/69 days	48	~340	McCollister *et al.*, 1964

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[*] Acrylamide mixed with food. Dose in mg/kg estimated by McCollister and coworkers, 1964.

[+] Effect noted in only 1/20 exposed animals.

[#] Signs of intoxication probably appeared earlier than noted. See text, p. 96.

[x] Signs of intoxication based on electrorod measurements. See text, p. 89.

feeding exposures are available on mice. These are discussed below. Information on acrylamide-induced neuropathy in guinea pigs is unpublished and has not been available for this review (see Spencer and Schaumburg, 1974b).

In early studies on acrylamide neuropathy, Kuperman (1957, 1958) noted that the gross toxic effects of acrylamide are related directly to the cumulative dose and are independent of the magnitude of the daily dose. This pattern will be referred to as Kuperman's generalization and is illustrated in Table 25.

Table 25. Development of Ataxia After Repeated Intraperitoneal Injections of Acrylamide to Cats (Kuperman, 1958)

Daily Dose	No. Cats	Cumulative Dose*	Time
mg/kg		mg/kg	days
1	5	101 ± 30	125 ± 26
2	7	132 ± 24	91 ± 18
5	3	78 ± 5	22 ± 3
10	8	126 ± 29	19 ± 6
15	5	102 ± 10	9 ± 11
25	11	102 ± 20	6 ± 2
40	6	73 ± 21	3 ± 1
50	3	100 ± 0	2 ± 0

* Mean ± per cent S.D.

Kuperman (1958) demonstrated that the onset of ataxia occurred after a mean dose of 102 mg/kg, and deviations from this mean approximated a normal distribution. As indicated in Table 24, subsequent exposures tend to support this relationship if dose schedules are comparable and the total exposure period is not protracted. However, as periods between dosing increase with subsequent increases in exposure periods, the relationship of toxic effect to total cumulative dose becomes less substantial. The results of Fullerton and Barnes (1966), summarized at the top of Table 24, show that rats tolerated 2.5 times the cumulative dose of acrylamide (as 100 mg/kg/dose) when administered once every 14 days as opposed to dosings once weekly or twice weekly. This apparent deviation from Kuperman's generalization, however, was attributed to the increased sensitivity of the older rats on the one dose/14 days schedule, rather than to an unusually delayed cumulative effect (see p. 99).

Kuperman (1957, 1958) also stated that the route of administration affects neither the dose required to produce a given effect nor the latent period of the effect. Based on the exposures summarized in Table 24 as well as the more detailed dose response data presented below, this generalization is also substantially correct. The apparent decreased cumulative dose, with intraperitoneal as opposed to oral administration, necessary to cause initial effects in rats at doses of 25, 30, and 40 mg/kg is an artifact of the technique used to determine the onset of effects. Fullerton and Barnes (1966) and McCollister and coworkers (1964), using oral administration, defined the onset of neurological effects as observable hind limb weakness. In the intraperitoneal exposures, however, Kaplan and coworkers (Kaplan and Murphy, 1972; Kaplan et al., 1973) used an electrorod to determine the onset of effects. This device measures the ability of a rat to maintain balance on a horizontal wooden rod while the rod is being rotated along the horizontal axis. In that the electrorod technique may be a more sensitive index of early neurological damage, the cumulative doses necessary to cause initial effects when measured by this technique should be lower than cumulative doses causing signs of hind limb weakness (Kaplan and Murphy, 1972; Kaplan et al., 1973). Thus, Kuperman's generalization that the cumulative dose is the overriding factor in the development of early signs of neurotoxicity in repeated exposures to acrylamide over periods of a few days to a few months seems valid. Exceptions to this generalization, involving prolonged exposures to sub-neurotoxic levels of acrylamide, are discussed at the end of this section (see p. 105).

Given Kuperman's generalization, Table 24 indicates that cats are more susceptible to acrylamide neuropathy than rats or primates. In most exposures, cats develop early signs of neuropathy after cumulative doses of 100-300 mg/kg acrylamide. For primates and rats, 300-600 mg/kg acrylamide is required to produce comparable effects. The cumulative doses (105-350 mg/kg) described for dogs in Table 24 resulted in a complex of clinical signs (Hamblin, 1956; Thomann et al., 1974; see also below, p. 96), indicating that initial effects - e.g., simple ataxia or hind limb weakness - appeared at lower cumulative dose levels. This suggests that dogs are at least as sensitive as cats. As indicated previously, comparable repeated dose data are not available for mice. In continuous feeding studies, acrylamide at 250 ppm in water caused clinical signs including hind limb scissoring in mice after 14-21 days (Asbury et al., 1973; Bradley and Asbury, 1970). Comparable exposures of rats to 300 ppm acrylamide resulted in hind limb weakness after 20-28 days (Hamblin, 1956; Hopkins and Lambert, 1972; McCollister et al., 1964; Tsujihata et al., 1974). This suggests that mice may be somewhat more susceptible than rats to acrylamide in continuous feeding exposures. However, because mice generally tend to consume more food per unit body weight than rats (e.g., Hoeltge Inc., 1973), the total cumulative doses required to produce clinical signs in these two mammals probably do not differ markedly. Therefore, based on the available data, the susceptibility of mammals to acrylamide neuropathy seems to be: cats ≈ dogs > mice ≈ rats and primates. However, given the variability evident in Table 24, this order should be seen only as a general trend. The actual differences in susceptibility between these groups of mammals are not substantial, and exceptions are readily apparent. For instance, at oral doses of 20 mg/kg/day, cats developed early signs of neuropathy after 14-21 days [280-420 mg/kg] (Leswing and Ribelin, 1969). On the same dose schedule, Hopkins (1970) noted hind limb weakness in a baboon after 16 days [320 mg/kg].

Clinical Signs of Intoxication

The gross signs of acrylamide intoxication have been most extensively described for rats. While hind limb weakness is most often cited as the first sign of repeated acrylamide exposure, growth inhibition and/or proprioceptive impairment may precede or coincide with the onset of hind limb debility. In rats given intraperitoneal injections of 50 mg/kg/day, slight weight loss was noted after 2-4 days. The weight of the exposed animals remained about 10% below control animals throughout the exposure period. During the fourth through sixth days of exposure, decreased proprioception was indicated by progressively increasing failures on the electrorod apparatus. Actual signs of ataxia were not evident until the seventh day of exposure [350 mg cumulative dose] (Kaplan and Murphy, 1972). Using the same route and dose schedule, Suzuki and Pfaff (1973) noted that both decreased weight gain and slight hind limb weakness appeared after five injections to young rats. On oral administration, only growth retardation was seen at 100 ppm for 42 days while both growth retardation and hind limb weakness appeared at 300 ppm for 28 days (Hamblin, 1956).

Loss of proprioception appeared concurrently with hind limb weakness after oral administrations of 9 mg/kg/day for 90 days and 30 mg/kg/day for 21 days. Response to painful stimuli, however, was not impaired (McCollister et al., 1964). As exposure proceeds, hind limb weakness becomes progressively more severe. On oral exposures of 200-300 ppm over periods of 5-27 weeks, ataxia, hind limb splay, dragging of hind limbs while attempting to walk, and flaccid hind limb weakness develop (Tsujihata et al., 1974; Morgan-Hughes et al., 1974). More severe exposures are generally fatal to at least some animals. At concentrations of 300-400 ppm over 24-42 weeks, most rats died after developing complete loss of hind-quarter control. Extreme protrusion of the penis was also noted in male rats (McCollister et al., 1964). Fore limb weakness has appeared in some rats after the development of hind limb paralysis (Hamblin, 1956; Suzuki and Pfaff, 1973; Tsujihata et al., 1974). In addition to severe weakness of the extremities, prolonged acrylamide intoxication commonly involves gross distention of the bladder (Fullerton and Barnes, 1966; McCollister et al., 1964; Suzuki and Pfaff, 1973) and reduced weight gain (Hamblin, 1956; Tsujihata et al., 1974). In severely poisoned male rats, degeneration of the testicular tubules has also been noted (McCollister et al., 1974).

A summary of these effects showing approximate dose-response relationships is given in Table 26. Given the variety of dosing schedules, routes of administration, and different experimental techniques used in these studies, the results are remarkably consistent. Growth retardation and proprioceptive impairments are evident after cumulative doses of 100-200 mg. Observable signs of hind limb weakness appear in rats after cumulative doses of 250-630 mg. At approximately twice this dose (600-12600 mg), signs of severe

Table 26. Effects of Repeated Acrylamide Exposure on Rats

Effect	Dose Schedule, Route	Cumulative Dose (mg/kg)	Reference
Mild - Moderate			
Growth retardation only	100 ppm x 42 days, oral	-	Hamblin, 1956
Onset of weight loss	50 mg/kg/day x 2-4 days, i.p.	100-200	Kaplan and Murphy, 1972
Growth retardation with hind limb weakness	300 ppm x 28 days, oral	-	Hamblin, 1956
Loss of proprioception with hind limb weakness	9 mg/kg/day x 90 days, oral	810	McCollister et al., 1964
" "	30 mg/kg/day x 21 days, oral	630	" "
Decreased electrorod performance	50 mg/kg/day x 4-6 days, i.p.	200-300	Kaplan and Murphy, 1972
Lowered weight gain and hind limb weakness	50 mg/kg/day x 5 days, i.p.*	250	Suzuki and Pfaff, 1973
Hind limb weakness	25 mg/kg/day x 20 doses, i.p.	500	Fullerton and Barnes, 1966
" "	50 mg/kg/day x 7-8 doses, i.p.	350-400	Suzuki and Pfaff, 1973
Hind limb weakness and ataxia	50 mg/kg/day x 6 doses, i.p.	300	Kaplan and Murphy, 1972
" "	200 ppm x 49-126 days, oral	-	Morgan-Hughes et al., 1974
" "	300 ppm x 35-49 days, oral	-	" "
" "	300 ppm x 20 days, oral	-	Tsujihata et al., 1974
Moderate - Severe			
Flaccid hind limb weakness	200 ppm x 77-189 days, oral	-	Morgan-Hughes et al., 1974
" "	300 ppm x 49-70 days, oral	-	" "
Loss of hindquarter control, protrusion of penis	30 mg/kg/day x 28 days, oral	840	McCollister et al., 1964
" "	40 mg/kg/day x 24 days, oral	960	" "
Hind limb drag, forelimb weakness, and weight loss	300 ppm x 30 days, oral	-	Tsujihata et al., 1974
Hind limb paralysis, fore limb weakness, and bladder distention	50 mg/kg/day x 15-17 doses, i.p.	750-850	Suzuki and Pfaff, 1973
Paralysis of all four limbs, weight loss, and death	50 mg/kg/day x 15 doses, i.p.	750	Hamblin, 1956
Severe weakness, bladder distention, death	50 mg/kg/day x 12 doses, i.p.	600	Fullerton and Barnes, 1966
" "	100 mg/kg/day x 6 doses/3 weeks, i.p.	600	" "
Severe weakness, bladder distention, protrusion of penis, testicular tubular degeneration, death	800 ppm x 7 days, 400 ppm x 21 days, oral	-	McCollister et al., 1964
Severe weakness, death, fatal to most animals	1000 ppm or 2500 ppm x 14-21 days, oral	-	Hamblin, 1956
" "	30 mg/kg/day x 42 days, oral	1260	McCollister et al., 1956

* young rats

intoxication are elicited. Where comparable dose schedules are used [e.g., 30 mg/kg/day, McCollister et al., 1956; 50 mg/kg/day, Kaplan and Murphy, 1972, and Fullerton and Barnes, 1966], the ratio of cumulative dose producing hind limb weakness to lethal cumulative dose is 2:1. The only dose-response relationship that markedly deviates from Kuperman's generalization is the 9 mg/kg/day for 90 days exposure reported by McCollister and coworkers (1964). As discussed below (see p.101), this deviation probably is attributable to an increase in the ability of animals to tolerate large cumulative doses of acrylamide when the chemical is administered in small daily amounts over prolonged periods. [This should not be confused with the increased susceptibility of animals due to age when large doses are administered over extended periods with long intervals between doses - see p. 99].

Similar extensive dose-response data are not available for the other mammals tested. However, the general progress of prolonged acrylamide intoxication in cats has been described in detail by a variety of investigators. The description given by Kuperman (1958) encompasses most of the signs noted by subsequent investigators. Hind limb weakness and ataxia followed by dysmetria are early signs of intoxication. The usual sequence of major signs in chronic intoxication is ataxia, hind limb weakness, dysmetria, progressive weakness of the voluntary muscles, hind limb drag, inability to move about, quadraparesis, and death (Hamblin, 1956; Prineas, 1969). While walking, cats often exhibit fore limb crossing with truncal sway and wide based gait (Schaumburg et al., 1974). Kuperman (1958) described tremors of the head and muscles which occurred when cats were stationary, as well as irregular tremors in the limbs which occurred during movement. Head tremors have also been described by Schaumburg and coworkers (1974), and a slight (unspecified) effect on head movements has been noted by Prineas (1969). Although hind limb drag can occur during severe intoxication (Leswing and Ribelin, 1969), proximal muscle strength in the hind limbs is not markedly affected even during hind limb drag (Sumner and Asbury, 1975). Foot drop, toe splay, and loss of tendon reflexes are also commonly noted in severe intoxication (Prineas, 1969; Schaumburg et al., 1974; Sumner and Asbury, 1975). Hoarse cries in advanced intoxication have been noted by both Prineas (1969) and Leswing and Ribelin (1969), suggestive of involvement of the laryngeal nerves [see p. 104 for pathological data]. As in rats, response to pain is not impaired even during extreme intoxication (Pleasure et al., 1969; Prineas, 1969; Leswing and Ribelin, 1969). Only Prineas (1969) describes loss of weight as well as fur loss in cats.

A summary of the available dose-response relationships in cats is given in Table 27. As in the rat exposures, an approximate 2:1 relationship is apparent in the ratio of cumulative doses required to produce mild as opposed to severe effects.

Table 27. Effects of Repeated Acrylamide Exposure on Cats

Effect	Dose Schedule, Route	Cumulative Dose (mg/kg)	Reference
Mild			
Hind limb weakness or ataxia	see Table 24	102	Kuperman, 1958
	20 mg/kg/day x 14-21 days, oral	280-420	Leswing and Ribelin, 1969
	10 mg/kg/day x 21-34	210-340	Sumner and Asbury, 1975
	20 mg/kg x 10-60 doses/14-42 days, oral	200-600	Bradley and Williams, 1973
	3 mg/kg/day x 5 days/week x 68 days	144	McCollister et al., 1964
	10 mg/kg/day x 5 days/week x 20 days	200	" "
	10 mg/kg/day x 17-22 days, s.c.	170-220	Prineas, 1969
	10 mg/kg/day x 13-15 days, i.p.	130-150	Schaumburg et al., 1974
	3 mg/kg/day x 70 - 163 days	210-489	
Moderate - Severe			
Moderate - severe hind limb ataxia	10 mg/kg/day x 38-44 days, s.c.	380-440	Sumner and Asbury, 1975
Gross incoordination of all limbs	10 mg/kg/day x 24-36 days, s.c.	240-360	Prineas, 1969
Foot drop, lack of tendon reflexes, hoarse voice, some loss of weight and fur	10 mg/kg/day x 40 days	400	Prineas, 1969
Distal muscle weakness and foot drop	3 mg/kg/day x 7 months	630	Schaumburg et al., 1974
Extreme hind limb ataxia, moderate fore limb ataxia	10 mg/kg/day x 47-67 days	470-670	Sumner and Asbury, 1975
Lack of control in all limbs, unable to stand	10 mg/kg/day x 5 days/week x 52 days, oral	170	McCollister et al., 1964
Decreased control of all limbs, barely able to walk	10 mg/kg/day x 28 days 20 mg/kg/day x 15 days	280 300	Schaumburg et al., 1974

Mice have seldom been used as experimental mammals in acrylamide neuropathy. Based on the available information, the quantitative signs of intoxication are similar to cats. When administered acrylamide in the drinking water at 250 ppm for 25 days, all mice developed hind limb weakness which included hind limb dragging in some animals. By 35 days, a hoarse squeak and some loss of weight and fur were evident (Bradley and Asbury, 1970).

The clinical picture in dogs is somewhat less clear. At oral doses of 10 mg/kg/day for 28-35 days, Hamblin (1956) noted hind limb weakness, ataxia, and general signs of hindquarter incoordination. More recently, however, oral doses of 5 mg/kg/day for 60 days have been shown to result in not only ataxia and weakness of the jaw muscles but also sedation. At 15 mg/kg/day for 22 days, normal hind limb effects were also accompanied by mydriasis, salivation, hypnosis, labored respiration, and convulsions. Because the dogs in the latter exposure group were shown to have suppurative lobular pneumonia, the above atypical effects cannot be directly attributed to acrylamide (Thomann et al., 1974)

The effects of acrylamide poisoning in primates have been studied using baboons (Hopkins, 1970; Hopkins and Gilliat, 1967; Hopkins and Gilliat, 1971) and monkeys (Leswing and Ribelin, 1969; McCollister et al., 1964). Generally, these mammals show signs of intoxication typical of the other mammals studied. Initially, ataxia and weakness of the hindquarters appear. Subsequently, weakness develops in the fore limbs and facial muscles (see Table 28). In addition, both baboons and monkeys experience difficulty in holding food during advanced intoxication (Leswing and Ribelin, 1969; Hopkins, 1970). Baboons show some signs of sensory impairment in that they sometimes behaved as if they were unaware that food had been dropped. However, they remained sensitive to pinprick. In addition, baboons lost 17-45% of body weight and tendon reflexes were abolished during prolonged exposures (Hopkins, 1970). Leswing and Ribelin (1969) inferred mandibular nerve involvement in severely poisoned monkeys which were unable to chew.

Table 28 summarizes the dose-response information from primate exposures. While the cumulative doses necessary to produce mild effects in primates do not differ radically from those of rats, the ratio of severe to mild cumulative doses is somewhat less in primates (~1.1 - 1.75).

Table 28. Effects of Repeated Acrylamide Exposure on Primates

Effect	Dose Schedule, Route	Cumulative Dose (mg/kg)	Reference
Mild			
Hind limb weakness	20 mg/kg/day x 16 days, oral	320	Hopkins, 1970
	15 mg/kg/day x 42 days, oral	630	" "
	10 mg/kg/day x 56-97 days, oral	560-970	" "
	10 mg/kg/day x 49 doses/69 days x 48 days, oral	340	McCollister _et al._, 1964
Severe			
Extreme hind limb weakness	10 mg/kg/day x 49 doses/69 days x 69 days, oral	490	McCollister _et al._, 1964
Severe hind limb weakness with fore limb weakness	20 mg/kg/day x 28 days, oral	560	Hopkins, 1970
	15 mg/kg/day x 73 days, oral	1095	" "
	10 mg/kg/day x 61-147 days, oral	610-1470	" "

In rats, mice, and cats, several investigators have noted periods during exposure in which gross signs of toxicity did not increase with increasing cumulative dose. In rats, Suzuki and Pfaff (1973) noted that young rats on a dosing schedule of 50 mg/kg (i.p.) x 3 doses/week x 30 days began to show recovery after 28 days in spite of continued injections. In oral administrations of 300 ppm x 125 days [estimated total dose of 1890 mg], rats developed severe hind limb weakness with moderate fore limb weakness after 56 days [840 mg]. Although several animals died after 56 days, the general signs of neurotoxicity did not increase (Hopkins and Lambert, 1972). In similar exposures to 250 ppm x 45 days to mice, Bradley and Asbury (1970) noted no increase in the severity of hind limb involvement after 35 days. Neither frank fore limb weakness nor death were seen in the total exposure period. A definite plateau response is also described by McCollister and coworkers (1964) for two cats on oral doses of 3 mg/kg/day x 5 days/week x 367 days. After day 68 (144 mg/kg), definite hind limb weakness had developed in both cats. However, by the end of the exposure period (cumulative dose of 771 mg/kg), no further decrease in hindquarter weakness was seen. The significance of these observations is questionable. Nevertheless, they do suggest that the onset of signs of severe acrylamide intoxication, unlike those of initial intoxication, are not directly dependent on total cumulative dose.

Recovery

In all mammals tested, even severe acrylamide intoxication is apparently reversible. Recovery from gross signs of intoxication is accompanied by the repair of structural damage and a return to normal nerve conduction velocity (see Sections ii, p. 103 and iii, p. 109 below). Table 29 partially summarizes recovery data in mammals.

Table 29. Recovery Periods In Mammals After Severe Acrylamide Intoxication

Organism	Duration of Exposure (Days)	Total Cumulative Dose (mg/kg)	*Days to Recovery After Last Day of Dosing	Reference
Rats	~ 21	600	21	Fullerton and Barnes, 1966
	~ 38	700	28	" "
	~ 56	800	(21)	" "
	~ 63	800	24	Suzuki and Pfaff, 1973
	~ 24	960	55	McCollister et al., 1964
	~ 42	1260	57	" "
	~ 63	1300	~60	Suzuki and DePaul, 1971
	~240	2400	~150	Fullerton and Barnes, 1966
	~392	2800	~180	" "
Cats	52	370	53	McCollister et al., 1964
Dogs	22	330	30	Thomann et al., 1974
Primates	29	380	63	Hopkins, 1970
	69	490	54	McCollister et al., 1964
	94	1410	364	Hopkins, 1970

* Recovery defined as decrease or absence of clinical signs of intoxication;

Parentheses ( ) indicate partial recovery

The period to recovery, at least in rats, correlates closely with the total cumulative dose rather than the period of dosing or magnitude of the daily dose used. In rats, Kaplan and Murphy (1972) have associated recovery with increased sciatic nerve β-glucuronidase activity. Rats given intraperitoneal injections of 50 mg/kg/day x 8 days exhibited decreased electrorod performance. After 30 days, a 340% increase above control activity was noted for this enzyme, which coincided with a return to normal electrorod performance. However, rats with elevated β-glucuronidase activity were significantly more susceptible to reexposure. A return to normal susceptibility required about 90 days, at which time β-glucuronidase activity was normal (Kaplan and Murphy, 1972).

Similar patterns are evident for other mammals, although the relationship of recovery to enzyme levels has not been studied. In cats, the period to recovery is directly related to the severity of intoxication. In the 53 day recovery period summarized in Table 29, the cats were unable to stand at the end of the exposure period (McCollister _et al_., 1964). In exposures involving only moderate to severe hind limb weakness, 31-36 days were required for complete recovery (Schaumburg _et al_., 1973). At the other extreme, cats kept severely intoxicated for prolonged periods did not recover fully even after several months (Leswing and Ribelin, 1969). The recovery data on primates in Table 29 suggest that these mammals recover more slowly than rats, even though primates and rats are about equally susceptible to acrylamide intoxication in terms of the cumulative dose required to produce hind limb weakness.

Influence of Age and Sex

The influence of age in the development of acrylamide neuropathy has been determined only in rats. For the most part, young animals are able to tolerate higher cumulative doses of acrylamide before signs of neurological damage appear. At intraperitoneal doses of 100 mg/kg/week x 4 weeks, Fullerton and Barnes (1966) found that groups of rats 5 and 8 weeks old developed mild symptoms, while 26 week old rats evidenced severe symptoms. Rats 52 weeks old were able to tolerate only three doses before the onset of severe symptoms. Similar age-response effects have been noted by Kaplan and Murphy (1972) in rats between 5 and 14 weeks old given intraperitoneal injections of 50 mg/kg/day. Table 30 summarizes this data with onset of effect and recovery defined as failure and reestablishment of normal electrorod performance.

Table 30. The Effect of Age on the Onset of and Recovery from Acrylamide Intoxication in Rats

(Data from Kaplan and Murphy, 1972)

Age of Rats* (Weeks)	Onset of Effects (Days ± SE)	Recovery Period (Days ± SE)
5	7.3 ± 0.22	19.2 ± 0.40
7	6.4 ± 0.22	15.6 ± 0.50
11	5.5 ± 0.20	13.8 ± 0.66
14	5.3 ± 0.19	14.8 ± 0.48

* Doses of 50 mg/kg/day, intraperitoneal; groups of 12 rats used.

The 5 week old rats were significantly more resistant than 11 and 14 week old rats to the onset of acrylamide intoxication ($p < 0.01$) but required a significantly greater period to recover than any of the older rats ($p < 0.01$). This increased recovery period in younger rats is probably attributable to the greater cumulative dose required to produce overt signs of toxicity rather than to impaired recovery processes in the younger animals. The increased ability of the younger rats to tolerate higher cumulative doses may be related to increased liver microsomal enzyme levels (Kaplan and Murphy, 1972; Kaplan et al., 1973). Only one study has shown greater susceptibility in younger rats. Using one-day old suckling rats, Suzuki and Pfaff (1973) noted the onset of adverse neurological effects after 5-6 doses of 50 mg/kg x 3 doses/week. Adult rats on the same dosing schedule evidenced initial signs of toxicity after 7-8 doses. These investigators attributed the increased susceptibility of very young rats to incomplete development of the barrier system of the peripheral nerves. The possibility that decreased levels of liver drug-metabolizing enzymes in very young rats might also be a factor in increased sensitivity was not explored. In any event, some one-day old rats, but no adult rats, showed signs of recovery during the six week exposure period. This would seem to suggest that the increased susceptibility is limited to very young rats (Suzuki and Pfaff, 1973).

Although no detailed studies are available, Fullerton and Barnes (1966) indicated that sex does not influence the response of rats to chronic acrylamide intoxication.

No Apparent Adverse Effect Levels

Table 31 summarizes acrylamide exposures which have no apparent adverse effects on mammals. At sufficiently low daily dose levels over prolonged periods of administration, mammals are not adversely affected by cumulative doses of acrylamide which are neurotoxic over shorter periods of administration. This can be illustrated by comparing mildly toxic exposures (Table 24, p. 87) to exposures producing no signs of toxicity (Table 31, p. 102). For rats, cumulative doses of 1323-2079 mg/kg given orally over six-month periods caused no signs of limb impairment. Less than this cumulative dose (560-630 mg/kg) given

Table 31. Acrylamide Doses Producing No Signs of Adverse Effects

Organism	Route	Dose, Schedule	Duration of Exposure in Days (Number of Doses)	Cumulative Dose (mg/kg)	Reference
RATS	Oral	3 mg/kg/day	90	270	McCollister et al., 1964
	Oral	10 mg/kg/day	70# (55)	550	Fullerton and Barnes, 1966
	Oral	10 mg/kg/day	≥116# (116)	1160	" "
	Oral	7 mg/kg/day*	189	1323	McCollister et al., 1964
	Oral	11 mg/kg/day*	189	2079	" "
	Oral	40 ppm	730	~2900 (see text)	Dow Chemical, no date
CATS	Oral	0.3 mg/kg/day	365(~260)	~78	McCollister et al., 1964
		1.0 mg/kg/day	367(257)	257	" "
DOGS	Oral	1 mg/kg/day	~133	133	Hamblin, 1956
	Oral	5 mg/kg/day	~ 35	175	" "
	Oral	8 mg/kg/day	~ 28	224	" "
PRIMATES	Oral	1 mg/kg/day	363(255)	255	McCollister et al., 1964
	Oral	3 mg/kg/day	363(255)	765	" "

* Acrylamide mixed with food. Dose in mg/kg estimated by McCollister and coworkers, 1964.

# Duration not specified. Minimum estimate of duration assumes 1 dose/day.

over periods of 2-3 weeks, however, resulted in obvious signs of hind limb weakness (McCollister et al., 1964). A similar, though less marked, comparison can be made for the results of Fullerton and Barnes (1966). Weil and McCollister (1963) summarized a study by Dow Chemical (no date) indicating that 40 ppm acrylamide in food had no effect on rats over a two-year period. Based on the conversion factors given by McCollister and coworkers (1964), this would be equivalent to a daily dose of 4 mg/kg and a total cumulative dose of about 2900 mg/kg. This is about six times the cumulative dose shown to have neurotoxic effects when administered over a period of about one month. Based on the results of Hamblin (1956) and McCollister and coworkers (1964) in Tables 24 and 31, similar relationships between duration of exposure and the effects of comparable cumulative doses are also apparent with cats, primates, and - to a lesser extent - dogs.

(ii) Acrylamide - Structural Changes

Acrylamide intoxication is accompanied by various morphological signs of nerve tissue deterioration. In the peripheral nerves, axonal degeneration with demyelination has been observed in mice (Bradley and Asbury, 1970), rats (Fullerton and Barnes, 1966; Suzuki and Pfaff, 1973), cats (Leswing and Ribelin, 1969; Prineas, 1969; Schaumberg *et al.*, 1974), dogs (Thomann *et al.*, 1974), baboons (Hopkins, 1970), and monkeys (Leswing and Ribelin, 1969). To date, axonal degeneration has been demonstrated only in myelinated fibers. Schaumberg and coworkers (1974) have found no evidence of unmyelinated axon degeneration in cats.

By light microscopy, the first sign of morphological deterioration appears to be nodal or paranodal axonal swelling - i.e., swelling at or near the nodes of Ranvier (Hopkins, 1970; Prineas, 1969; Schaumburg *et al.*, 1974; Spencer and Schaumburg, 1974b). Electronmicroscopic examinations have characterized these swellings as masses of neurofilaments, various dense bodies, and either enlarged or degenerating mitochondria (Prineas, 1969; Schaumburg *et al.*, 1974; Suzuki and Pfaff, 1973). After initial swelling, the myelin sheath retracts paranodally along the axon. Subsequent to myelin retraction, actual axonal degeneration occurs and may be accompanied by myelin fragmentation (Hopkins, 1970; Prineas, 1969; Schaumburg *et al.*, 1974). Extensive myelin breakdown, as opposed to retraction, occurs only after axonal degeneration (Fullerton and Barnes, 1966). This may in part account for the wide variety of myelin involvement - which may range from severe (e.g., Bradley and Asbury, 1970; Leswing and Ribelin, 1969) to minimal (e.g., Hopkins, 1970) - in animals with comparable clinical signs of acrylamide intoxication.

Damage to the peripheral nerves is invariably more severe distally than proximally. Paralleling the clinical signs of intoxication, hind limb nerves seem to be the most severely affected. In rats, nerve fiber degeneration is first seen in the plantar sensory nerves of the hindfeet and branches of the tibial nerves supplying the calf muscles (Spencer and Schaumburg, 1977). Fullerton and Barnes (1966) noted marked decreases in fiber density in the sural and posterior tibial nerves in the species, but only a moderate decrease in density in the sciatic nerve. Similar patterns of increasing damage progressing distally along the hind limb nerves have been noted in mice, cats, dogs, and primates (Bradley and Asbury, 1970; Hopkins, 1970; Leswing and Ribelin, 1969; Prineas, 1969; Schaumburg et al., 1974; Suzuki and Pfaff, 1973; Thomann et al., 1974). However, the extent of hind limb nerve damage may vary in different species showing comparable signs of intoxication. In severely poisoned mice, Bradley and Asbury (1970) noted myelin breakdown in over 50% of the fibers of the sciatic nerve. In cats with equally severe clinical signs, only a minority of fibers in the tibial nerve evidenced morphological damage (Prineas, 1969). Fore limb nerves also undergo axonal degeneration, but generally to a lesser degree than the hind limbs. In rats showing moderate to severe hind limb damage, axonal degeneration was seen in the median and ulnar nerves of the fore limb. In only one rat did the extent of median nerve damage approximate that seen in the sciatic nerve of the thigh (Fullerton and Barnes, 1966). In both monkeys and cats, fore limb nerve damage was consistently less severe than hind limb damage (Leswing and Ribelin, 1969). In addition to nerve damage of the limbs, Hopkins (1970) noted axonal degeneration of the recurrent laryngeal nerve. As with the limb nerves, damage was more severe distally.

Although distal to proximal degradation is the overall pattern of acrylamide neuropathy, both Hopkins (1970) and Prineas (1969) have noted that, in a given area along a single nerve trunk, damage to the various nerve fibers may differ markedly. This implies that certain nerve fibers are more susceptible than others. Consistent with these findings, Schaumburg and coworkers (1974) have demonstrated that Pacinian corpuscles (sensory nerve terminals) are somewhat more rapidly affected than distal primary sensory fibers of muscle spindle. Further, both of these sensory terminals are affected much more rapidly than neuromuscular junctions. However, neuromuscular junctions have been shown to undergo marked degeneration in acrylamide poisoning (Prineas, 1969; Tsujihata _et_ _al_., 1974). This damage and consequent muscle denervation probably account for the muscular atrophy noted in many instances of acrylamide intoxication (Fullerton and Barnes, 1966; Leswing and Ribelin, 1969; Prineas, 1969; Morgan-Hughes and coworkers, 1974). The sensitivity of nerve fibers to acrylamide is somewhat dependent on fiber diameter, but the precise relationship of diameter to sensitivity may be species specific. In the tibial nerves of normal rats, Fullerton and Barnes (1966) noted a unimodal distribution of diameter with the peak at 8-9 μ and a range of 2-14 μ. In severely poisoned rats, the 8-9 μ peak was eliminated suggesting that these medium-sized fibers are most severely affected (see Figure 15). In baboons - which normally show a bimodal distribution with peaks at 3 μ and 11 μ and a minimum at 7 μ - larger diameter fibers (10-16 μ) show the most pronounced dose-related decrease after acrylamide exposure, while medium-sized fibers stay the same or increase (Hopkins, 1970) [see Figure 16]. Although comparable data are not available for other species, Schaumburg and coworkers (1974) have noted that large diameter fibers are affected first in cats. Recent electrophysiological studies in dogs (see next section) also suggest that large fiber diameter axons are the most rapidly affected (Sumner and Asbury, 1975).

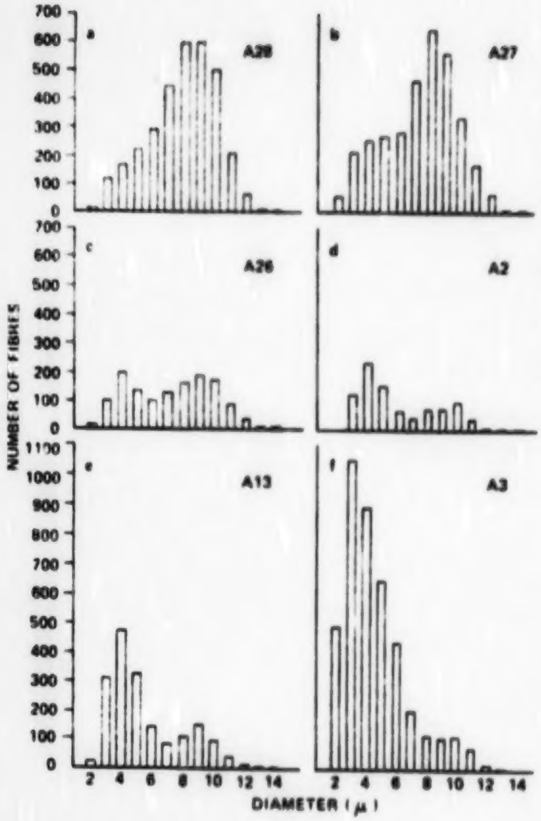


Figure 15. Histograms Showing Distribution of Diameters of All Myelinated Fibers in Posterior Tibial Nerves of Animals on the Following Diets: (a) and (b) healthy adult rats; (c) 400 ppm acrylamide for two months; (d) 300 ppm acrylamide for four months; (e) 200 ppm acrylamide for six months; (f) 300 ppm acrylamide for four months, followed by normal diet for six months.

(Fullerton and Barnes, 1966)

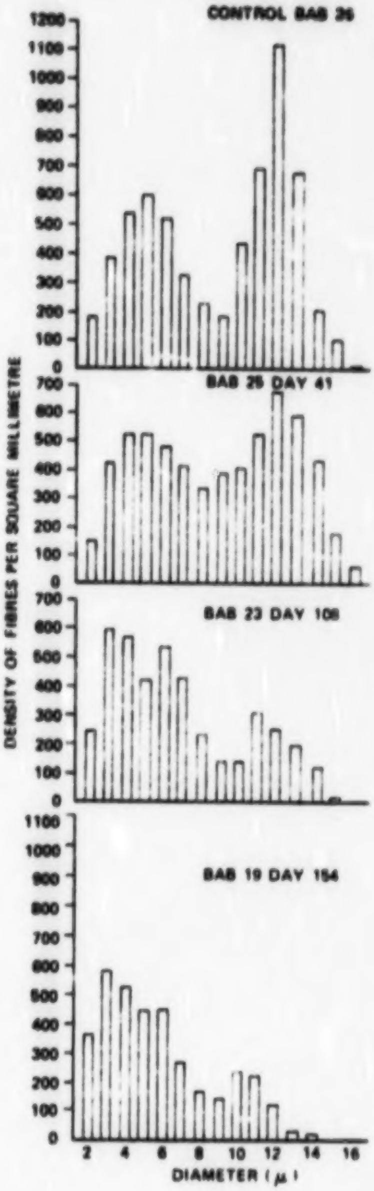


Figure 16. Histograms Showing Distribution of Diameters of Myelinated Fibers in the Sural Nerves (Ankle) of One Control Baboon (Bab. 26) and Three Baboons Intoxicated with Oral Doses of Acrylamide as Follows: Bab. 23, 10 mg/kg/day x 89 days + 19 days recovery; Bab. 19, 10 mg/kg/day x 137 days + 17 days recovery; Bab. 25, 10 mg/kg/day x 10 days.

(Hopkins, 1970)

Recovery from acrylamide intoxication is followed by peripheral nerve tissue regeneration. Such regeneration has also been reported to accompany intoxication (Suzuki and Pfaff, 1973). Increases in the number of small diameter fibers, as well as a general decrease in internodal length (distance between adjacent nodes of Ranvier) for fibers of a given diameter, have been used as indices of regeneration (see Fullerton et al., 1965). Rats, fed 300 ppm acrylamide for four months and allowed to recover for six months, no longer evidenced clinical signs of adverse effects. As previously discussed, this exposure caused an elimination of the normal 8-9 μ peak in nerve fiber diameter. After the recovery period, this peak was still absent, but a large peak appeared in the 3-4 μ diameter range. Further, a marked decrease in internodal length was apparent in fibers of 4-8 μ (Fullerton and Barnes, 1966, see Figure 17).

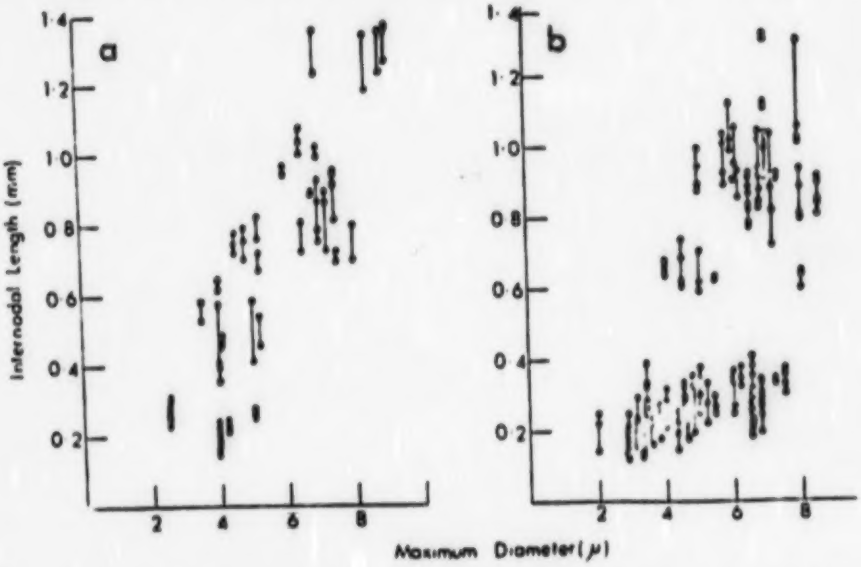


Figure 17. Internodal Length and Fiber Diameter in Posterior Tibial Nerve of (a) Normal Rats, (b) Rats A_3 and A_4 on 300 ppm Acrylamide for Four Months, Followed by Normal Diet for Five to Six Months. Values for different internodal lengths of the same fiber are joined by a line. These are plotted against the diameter of the largest internodal segment of the fiber concerned. (Fullerton and Barnes, 1966) (Reprinted with permission from P.M. Fullerton and J.M. Barnes, the British Journal of Industrial Medicine, Ed. R.I. McCallum, and the British Medical Association)

Similar patterns have been noted in baboons allowed to recover for a few months after severe intoxication. After two years, fiber density returned to normal, but fiber diameter was only two-thirds of preexposure values (Hopkins, 1970).

Several investigators have found no, or very little, indication of central nervous system damage from subacute or chronic acrylamide intoxication (Bradley and Asbury, 1970; Hamblin, 1956; Leswing and Ribelin, 1969; McCollister et al., 1964; Thomann et al., 1974). However, Prineas (1969) as well as Ghetti and coworkers (1973) have found pathological changes in both the spinal cord and brain of cats with chronic acrylamide intoxication. Prineas (1969) has noted degeneration in the ventral and lateral columns of the spinal cord and in the dorsal spinocerebellar tract of the medulla. Ultrastructurally, these changes are accompanied by accumulations of neurofilaments, mitochondria, and other dense bodies similar to those seen in the peripheral nerves. These observations have been confirmed by Ghetti and coworkers (1973), who have also noted similar pathological changes in the cerebellar vermis. These changes correspond to distal axonal degeneration of long descending and ascending spinal cord tracts, analogous to the pathological picture seen in the peripheral nervous system (Spencer and Schaumburg, 1976).

A less direct indication of central nervous system involvement is cited by Hopkins (1970), who found that in one baboon which lost the use of all four limbs, morphological damage to the peripheral nerves was minimal. In conjunction with the electrophysiological finding detailed below (see p. 110), Hopkins (1970) concluded that at least some central nervous system damage had occurred.

Damage to other tissues has not been seen in acrylamide intoxication. Fullerton and Barnes (1966) noted no abnormalities of the kidney, spleen, pancreas, suprarenal, and lungs in rats with severe neurological signs. In one year feedings to monkeys at 0.3-3.0 mg/kg/day, kidneys and liver appeared normal (McCollister et al., 1964).

(iii) Acrylamide - Functional Changes

Prolonged acrylamide intoxication has been shown to cause decreased conduction velocity and amplitude of peripheral nerve and muscle fiber, as well as increases in refractory period and chronaxy. As in morphological changes, unmyelinated fibers are unaffected (Hopkins and Lambert, 1972). Although conduction velocity has been most frequently used in electrophysiological studies of acrylamide neuropathy, it is a poor indicator of early pathological changes (Thomann et al., 1974). Even after the onset of mild ataxia, nerve conduction velocities are not significantly changed (Fullerton and Barnes, 1966; Leswing and Ribelin, 1969; Thomann et al., 1974). Lowndes and Baker (1976) have demonstrated that decreased conduction velocities in motor nerves are preceded by functional changes at the level of the nerve terminal. Sumner and Asbury (1974a) have also shown that acrylamide causes a functional block of nerve terminals of muscle stretch afferents. However, in severe exposures, decreased conduction velocities can be used as an index of intoxication. In rats showing severe hind limb debility, conduction velocity of motor fibers supplying the hind limb decreased to 80% of the control value. Similar decreases have been noted in hind limb nerves of dogs (70% of control value, Thomann et al., 1974), cats (72%, Leswing and Ribelin, 1969), baboons (51-70%, Hopkins and Gilliatt, 1967 and 1971), and monkeys (78%, Leswing and Ribelin, 1969). Consistent with clinical and pathological findings, hind limb nerves are more severely affected than fore limb nerves (Hopkins and Gilliatt, 1971; Leswing and Ribelin, 1969).

The relatively mild decrease in conduction velocity - 80% of control - noted by Fullerton and Barnes (1966) suggested that fast nerve fibers were preferentially attacked. This would be consistent with pathological findings which indicate that large diameter nerve fibers are the first to undergo degeneration. Sumner and Asbury (1975), using single fiber preparations of cat muscle stretch receptors, have recently demonstrated that fast conducting fibers (Group I, 72-126 m/sec) are more severely affected than slow conducting fibers (Group II, 24-72 m/sec). Further supporting pathological findings, Sumner and Asbury (1974b, 1975) have shown that sensory (A-alpha) fibers are markedly more susceptible to acrylamide than motor (A-delta) fibers. The increased susceptibility of sensory over motor neurons has also been demonstrated in the median nerve of baboons (Hopkins and Gilliatt, 1971).

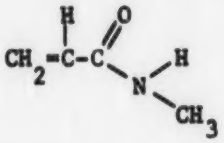
In recovery, a lag period has been noted between discontinuation of acrylamide and return of normal electrophysiological measurements. In the saphenous nerve of dogs, both refractory period and chronaxy increased during the first ten days of recovery. By day 30 of recovery, nerve conduction and chronaxy had returned to normal, although refractory periods were still abnormally long (Thomann et al., 1974). Similar lags lasting for several weeks have been noted in the recovery of cats, monkeys, and baboons (Leswing and Ribelin, 1969; Hopkins and Gilliatt, 1971). In cats recovering from severe intoxication, conduction velocities were still depressed after 2-3 months (Leswing and Ribelin, 1969). Normal conduction velocities returned in rats 5-9 months after exposure (Fullerton and Barnes, 1966). Similar to onset patterns, fore limb and motor nerves recover more quickly than hind limb and sensory nerves, respectively (Hopkins and Gilliatt, 1971).

Some electrophysiological studies imply central nervous system involvement. Based on asynchronous high-frequency EEG patterns of chronically intoxicated cats, Kuperman (1958) suggested brain stem damage. Hopkins (1970) also suggested central nervous system involvement in a baboon that became tetraplegic after oral doses of acrylamide at 20 mg/kg/day for 29 days. The median and anterior tibial nerves of this animal showed no decrease in conduction velocity, and the amplitude of the muscle action potential was normal. In view of the atypical pathological changes noted previously (see p. 108), Hopkins (1970) concluded that peripheral nervous system effects could not account for the limb disability. Similar conclusions have recently been proposed by Kuperman and Sunbhanich (1972). These investigators report that decreases in amplitude and conduction velocity of A-alpha fibers did not worsen with progressively worsening clinical signs. Further, the neurophysiological effects correlated with the magnitude of the daily dose, whereas the clinical signs of toxicity correlated with the cumulative dose.

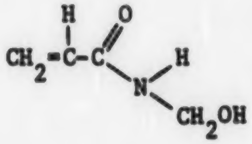
(iv) Acrylamide Analogs

Of the acrylamide analogs thus far tested, none approaches acrylamide in neurotoxic potency and most appear to be inactive. However, at least three acrylamide analogs have neurotoxic properties similar or identical to those of acrylamide, and two additional analogs seem to exert neurological effects. Those with acrylamide-like activity are:

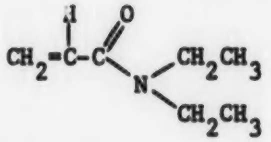
N-methylacrylamide,



N-methylolacrylamide,

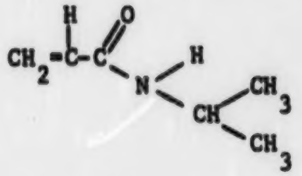


N,N-diethylacrylamide

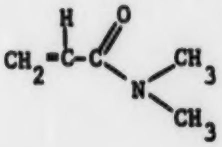


Analogs with neurological effects not yet completely defined are:

N-isopropylacrylamide,



N,N-dimethylacrylamide



Barnes (1970) and Edwards (1975b) have studied the effects of the first three acrylamide-like neurotoxins. Conflicting experimental results have been obtained on the neurotoxicity of N-methylolacrylamide. Using male Porton rats of approximately 200 g in weight, Edwards (1975b) found that a daily dose in chow at levels of 1800 ppm (27 mg/rat/day or 135 mg/kg/day) for one week followed by 900 ppm (18.6 mg/rat/day or 93 mg/kg/day) for four weeks produced slight ataxia (cumulative dose approximately 3543 mg/kg, 35 day exposure). Over the next two weeks, exposure to 900 ppm in diet plus four intraperitoneal injections at 50 mg/kg produced moderate ataxia (approximate cumulative dose of 5045 mg/kg, 49 day exposure). The clinical symptoms were identical to those of acrylamide. Barnes (1970) has noted only fine tremors in rats given seven oral doses of N-methylolacrylamide at 100 mg/kg followed by doses of 200 mg/kg on days 23 and 24 (cumulative dose 1100 mg/kg, 24 day exposure). However, rats given N-methylolacrylamide in the diet at levels of 400 ppm x 14 weeks, followed by 800 ppm x 7 weeks, followed by 1600 ppm x 6 weeks, did develop signs of hind limb weakness. The results were somewhat equivocal because acrylamide contamination could not be ruled out. Using purified N-methylolacrylamide, Hashimoto and

Aldridge (1970) were unable to detect signs of neurotoxicity in rats fed 1400 ppm x 1 week followed by 700 ppm for seven weeks (estimated cumulative dose of 4500-5400 mg/kg). However, such exposure to N-methylolacrylamide did increase the sensitivity of rats to acrylamide injections. Similar increases in sensitivity to acrylamide from preexposure to N-methylolacrylamide have been noted by Edwards (1975b) who suggests that the effect is additive rather than synergistic. Edwards (1975b) concludes that the failure of Hashimoto and Aldridge (1970) to induce neuropathic signs with the hydroxy-derivative was due to the low concentrations used. However, the cumulative doses administered in these two studies do not differ markedly.

Both Edwards (1975b) and Barnes (1970) have found N-methylacrylamide neurotoxic to rats. At 980 ppm in chow (approximate intake of 19 mg/rat/day or 95 mg/kg/day), slight hind limb disability was produced after 4-5 weeks [cumulative dose approximately 2660-3325 mg/kg over 28-35 days]. After 7-8 weeks, moderate disability was noted [approximate cumulative dose of 4655-5320 mg/kg over 49-56 days] (Edwards, 1975b). In the dosing schedule outlined below, Barnes (1970) also noted clinical signs similar to mild acrylamide intoxication in rats:

400 ppm x 10 weeks, oral
followed by 800 ppm x 3 weeks, oral
followed by 100 mg/kg x 7 doses in 14 days, oral
followed by 50 mg/kg x 10 doses, oral > 3 week period
followed by 100 mg/kg x 11 doses, oral

Edwards (1975b) has shown that N,N-diethylacrylamide produces signs in rats similar to those of acrylamide. Levels of 800 ppm in chow (approximate intake of 19 mg/rat/day or 95 mg/kg/day) had no effect after 10 weeks [approximate cumulative dose of 6650 mg/kg in 70 days]. However, continued exposure on a diet of 1600 ppm (39 mg/rat/day or 195 mg/kg/day) resulted in slight ataxia after two additional weeks [approximate cumulative dose of 9380 mg/kg in 84 days]. Slight ataxia was also produced after 8-10 weeks in chow containing 980 ppm N,N-diethylacrylamide (23 mg/rat/day or 115 mg/kg/day; approximate cumulative dose of 6440-8050 mg/kg in 56-70 days). Exposure at the same level for three additional weeks followed by two intraperitoneal injections of 90 mg/kg in the next week led to moderate disability within 2-4 days [approximate cumulative dose of 10,645 mg/kg in 91 days] (Edwards, 1975b). However, Barnes (1970) found no neurotoxic or other adverse effects in rats on the following dose schedule:

400 ppm x 10 weeks, oral
800 ppm x 3 weeks, oral
100 mg/kg x 7 doses over the next two weeks

This failure to note neuropathy is probably attributable to the lower cumulative dose in this exposure. Barnes (1970) regrettably does not supply estimates of food consumption. If the possibly tenuous assumption is made that rats in these two studies consumed about the same amount of food, the total cumulative dose in rats exposed by Barnes (1970) would equal 5775 mg/kg over 105 days. At a higher cumulative dose level (6650 mg/kg, see above), Edwards (1975b) also notes no signs of neuropathy. Thus, the results of these two studies may not be contradictory. As with the other acrylamide-like neurotoxins, N,N-diethylacrylamide enhanced acrylamide toxicity. Data on the degree of enhancement of acrylamide toxicity for all three compounds are summarized in Table 32. Thus, three N-substituted acrylamide derivatives - N-methylacrylamide, N-methylolacrylamide and N,N-diethylacrylamide - seem to have neuropathic activity similar to acrylamide and have an additive effect with acrylamide on the development of neuropathy (Edwards, 1975b).

Table 32. Effect of Acrylamide Analogs on the Development of Acrylamide Neuropathy

(Edwards, 1975b)

Compound	Concentration in diet (ppm)	No. of Weeks on Special Diet Before Acrylamide	Symptoms After Number of Doses of Acrylamide Shown						
			1	2	3	4	5	6	7
None	---	---					Slight	Slight	Moderate
N-Methylolacrylamide	1800 for 1 wk then 900	1	Slight	Slight	Moderate	Moderate	Moderate		
N,N-Diethylacrylamide	800	1					Slight	Moderate	Moderate
	980	3			Slight	Slight	Moderate	Moderate	Moderate
N-Methylacrylamide	980	3	Slight	Moderate	Moderate				

Rats were fed throughout the experiment on a diet of 41B powder containing test compounds at the concentrations shown. Intraperitoneal doses of acrylamide (50 mg/kg) were given twice a week (compounds 1, 2, 3, and 8) or three times a week (compounds 4, 9, and 10) beginning one or three weeks after commencing the special diet. Control rats having no addition to the diet became ataxic after the same total number of doses of acrylamide, whether these are given two or three times a week. The number of doses required to produce slight or moderate ataxia is taken as the number of doses to produce these symptoms in at least 50% of the rats.

Edwards (1975b) has compared the neurotoxic potencies of these acrylamide derivatives to acrylamide using equitoxic doses. This comparison, summarized in Table 33, indicates that N-methylolacrylamide is more potent than N-methylacrylamide.

Table 33. Comparative Potency of Neurotoxic Analogs to Acrylamide Based on Oral Exposures of Nine to Fourteen Days

(Edwards, 1975b)

	N-Methylolacrylamide	N-Methylacrylamide	N,N-Diethylacrylamide
Dose of analogue	35	91	134
Equivalent dose of acrylamide	7-10	10	3
Approximate potency based on equipotent doses (Acrylamide = 1)	.30	.13	.04

However, in the longer exposures described previously, N-methylacrylamide induced early signs of neuropathy in 28-35 days with cumulative doses of 2660-3325 mg/kg, while N-methylolacrylamide produced slight ataxia only after 35 days with a cumulative dose of 3543 mg/kg. Thus, the relative potencies of these two acrylamides on subacute exposure is not clear.

Unpublished studies summarized by Fassett (1963) seem to suggest that both N,N-dimethylacrylamide and N-isopropylacrylamide may also have neurological effects. A total dose of 840 mg/kg given intraperitoneally to cats over an 18 day period produced paralysis of hindquarters and head tremors. Although hind limb involvement is suggestive of acrylamide intoxication, no period of ataxia or simple hind limb weakness is described. Similarly, a cumulative dose of 540 mg/kg N,N-dimethylacrylamide given intraperitoneally to cats over about a two week period resulted in weight loss, tremors, slight spasticity, and difficulty in walking. However, the typical signs of acrylamide intoxication were absent. Nevertheless, these latter two compounds seem suspicious, both because the neurological signs are not greatly dissimilar to those of acrylamide and because these compounds are structurally quite similar to N-substituted acrylamide analogs with acrylamide-like neurotoxicity.

Five additional acrylamides are apparently not neurotoxic at the dose levels tested. Available details of these exposures are summarized in Table 34. Methylenebisacrylamide at levels of 1800 ppm in chow caused weight loss and signs of poor general health in rats. At this level, food intake was reduced, and the rats consumed only about 115 mg/kg/day (23 mg/rat) of the acrylamide. When the concentration was lowered to 900 ppm in chow, food consumption rose, weight stabilized, and the total daily intake of the chemical was 105 mg/kg (21 mg/rat). In a different exposure series, rats given 50 mg/kg/day x 5 days/week x 3 weeks showed no neurotoxic signs but did not gain weight (Edwards, 1975b).

Table 34. Acrylamide Analogs Without Apparent Neurotoxic Activity to Rats

Compound*	Dose Schedule, Route	Approximate Cumulative Dose (mg/kg)	Reference
Methacrylamide	50 mg/kg x 10 doses/11 days, oral then 100 mg/kg x 10 doses/14 days, oral	1500	Barnes, 1970
Methylenebisacrylamide**	115 mg/kg/day x 1 week, oral then 105 mg/kg/day x 10 weeks, oral	8155	Edwards, 1975b
N,N-Pentamethylenebisacrylamide	170 mg/kg/day x 6 weeks, oral	7140	Edwards, 1975b
N-*tert*-butylacrylamide	no details available	--	Fassett, 1963
N-*tert*-octylacrylamide	no details available	—	Fassett, 1963

* No adverse effects unless otherwise noted

** See text for adverse effects

A number of additional chemicals structurally related to acrylamide have shown no apparent neurotoxic or other adverse effects on subacute or oral exposure to rats. These include sodium acrylate, acrylonitrile, crotonamide, senecioic acid amide, allyl acetamide (Barnes, 1970), methyl methacrylate, ethyl crotonate, N-bis-acrylamido-acetic acid, 3,3'-iminodipropionamide, and 5-β-propionamido-glutathione (Edwards, 1975b).

e. Sensitization, Repeated Doses

Although many of the acrylamides are skin irritants to both laboratory mammals and man (see Sections III-B-2-c, p. 78 , and III-B-1-a, p. 63), sensitization has not been reported. Fassett (1963) indicates that N,N-dimethylacrylamide is not a skin sensitizer in guinea pigs. Specific studies on sensitization for the other acrylamides have not been encountered.

f. Teratogenicity

Edwards (1976) administered acrylamide to pregnant rats at dietary levels of 200 ppm and 400 ppm from the day of mating until parturition. Although the pregnant rats evidenced signs of acrylamide intoxication, the offspring had no macroscopic skeletal or organ abnormalities attributable to acrylamide exposure. Similarly, the offspring of pregnant rats given single intraveneous injections of acrylamide at 100 mg/kg on day 9 of gestation had no macroscopic or microscopic abnormalities in the brain, spinal cord, or sciatic nerve. No signs of nervous system damage were seen in any of the offspring even though transplacental transport of acrylamide was demonstrated.

g. Mutagenicity

No studies encountered.

h. Carcinogenicity

Tests specifically designed to determine the carcinogenic potential of the acrylamides have not been conducted. Although no tumors have been noted in chronic exposure studies described previously (see p. 108 , last paragraph), detailed pathological examinations have been confined primarily to nerve tissue.

The possible relationship between the alkylating ability of acrylamide and potential carcinogenicity has not been discussed in the literature. As described in Section III-B-2-a (p. 73), very small quantities of ^{14}C-labeled RNA and DNA are evident in rat brain and liver 24 hours after exposure to ^{14}C-labeled acrylamide. However, the levels of apparent incorporation into DNA were exaggerated by unspecified levels of ^{14}C-labeled protein contamination. In addition to this questionable binding of acrylamide to nucleic acids, acrylamide is extensively bound to protein and has been shown to alkylate with protein sulfhydryl groups (see p. 126). Although the mechanism of chemical carcinogenesis is not known, the ability to alkylate nucleic acids is a property common to many carcinogens (Clayson, 1975; Roberts, 1975). The degree of carcinogen binding to DNA is often very slight. For instance, 10 hours after intraperitoneal injections of urethan at 668 mg/kg to mice, the extent of binding to liver DNA is 9.3×10^3 moles nucleotides/mole urethan. Similarly, 120 hours after intraperitoneal injections of ethionine at 4.2 mg/kg to rats, the extent of binding to liver DNA is 2.7×10^7 moles nucleotides/mole ethionine (Sarma et al., 1975). In terms of nmoles carcinogen/mg DNA, the levels of incorporation of urethan and ethionine are about 3×10^{-1} and 1×10^{-4}, respectively. The apparent level of acrylamide incorporation into rat liver DNA after 24 hours was 1.6×10^{-2} nmoles acrylamide/mg (p. 73). Although alkylation of protein is a much less valuable index of carcinogenic potency (Sarma et al., 1975), it has proved useful in some experimental systems (Clayson, 1975; Heidelberger 1973). For example, in studies on the binding of various compounds to ligandin, a binding protein in rat liver, Litwack and coworkers (1971) found that the carcinogens tested differed from other compounds in that they formed covalent bonds with sulfur of cysteinyl groups. As indicated above, acrylamide forms covalent bonds with some protein sulfhydryl groups. While this type of data can in no way be construed as direct evidence of acrylamide carcinogenicity, it does suggest the need for further testing.

Acrylamide and certain acrylamide derivatives have been suggested as antitumor agents. Acrylamide has been shown to suppress the development of adenocarcinomas in dogs (Tsou et al., 1967) and sarcomas in mice (Kozlov and Dobrin, 1966). The inhibition of plant tumors is discussed in Section III-B-5,

p. 123. N, N'-methylenebisacrylamide has also been found to inhibit the development of transplanted mouse tumors (Tomcufcik et al., 1961). The mechanism of this tumor inhibition is not known. However, some antitumor agents are themselves alkylating agents (Stock, 1975). Consequently, many antitumor agents have significant carcinogenic activity (Harris, 1976).

i. Behavioral Effects

A number of investigators have noted behavioral changes in laboratory animals during acrylamide intoxication. However, such changes seem to have been tangential to the interests of these investigators and have not been described in great detail. In acutely poisoned rats (120 mg/kg, intraperitoneally), fright and excitement were noted prior to the onset of ataxia and convulsions (Druckrey et al., 1953). A variety of behavior effects described as "ranging from the development of fearful apprehension to viciousness" were seen in cats after subacute intoxication with acrylamide, while "behavior suggestive of hallucinations" was noted in acute exposures (Kuperman, 1958). After 35 days exposure to 250 ppm acrylamide in drinking water, mice with severe hind limb effects "appeared jittery" (Bradley and Asbury, 1970).

No permanent behavioral effects have been described in animals showing clinical signs of recovery from acrylamide intoxication.

j. Possible Synergisms and Other Drug Interactions

A number of factors have been examined for effects on acrylamide neuropathy. Hashimoto and Ando (1971) have found that administration of methionine reduces the neurotoxic potency of acrylamide. Kaplan and coworkers (1973) indicate that pyridoxine and thiamine deficient rats and rats injected with cortisol show no increased sensitivity to acrylamide. However, induction of microsomal enzymes with DDT or phenobarbital results in a markedly greater increase in the total cumulative dose necessary to cause electrorod failure. The effect of phenobarbital protection is illustrated in Table 35.

Table 35. Phenobarbital Protection in Acrylamide-Treated Rats (Kaplan *et al.*, 1973)

Acrylamide (mg/kg/day)	Phenobarbital[a] (50 mg/kg/day)	Mean Day For		Total Cumulative Dose (mg/kg)
		Onset	Recovery	
30	-	10.7 ± 0.36	23.4 ± 0.69	390
40	-	6.7 ± 0.33	18.0 ± 0.57	360
40	+	12.3 ± 0.47	28.1 ± 0.67	600
60	+	6.0 ± 0.40	17.6 ± 0.63	480

[a] Phenobarbital started 5 days before and continued simultaneously with acrylamide.

Corresponding increases in recovery time with increased cumulative dose was seen in the 40 mg/kg/day dose group. As described above, similar prolonged recovery patterns were also noted in young rats tolerating high cumulative doses (Kaplan and Murphy, 1972). Edwards (1975a), however, has found that neither DDT nor phenobarbitone affects the onset of neuropathic effects in rats on diets containing 500 ppm acrylamide. Further, doses of vitamin A (5000 IUm/kg) and vitamin E (52 IUm/kg) did not affect the response of rats to intraperitoneal injections of acrylamide [50 mg/kg x twice weekly].

As discussed in Section III-B-2-d-iv (p. 115), various neurotoxic acrylamide analogues have additive, but not synergistic, effects when administered with acrylamide.

k. Field Studies

None encountered.

3. Effects on Other Vertebrates

Acrylamide given orally at doses of 50 mg/kg/dose three times a week caused ataxia and weakness in nine adult Star Cross hens after four to nine doses. Clinical signs of toxicity were not reflected in histological damage to the peripheral nerves. In hens with severe ataxia, light microscopic examination of the sciatic, peroneal, and brachial nerves revealed only slight axonal degeneration. Central nervous system damage included some degeneration of the cervical spinocerebellar tracts and the medulla. Brain esterase activity was not inhibited in one ataxic hen when measured twenty-four hours after the last dose. Four severely ataxic hens showed complete clinical recovery after two to three months (Edwards, 1975b).

Male frogs (Rana temporaria) are also adversely affected by acrylamide but did not develop signs of neuropathy. Three of five animals died after three injections of 50 μg/g (50 mg/kg) into the dorsal sac. Two of three frogs died after a two-hour immersion in a 2% (v/v) aqueous solution of acrylamide. However, survivors from both of these exposures showed no adverse effects (Edwards, 1975b).

In static exposures of fathead minnows to acrylamide, 96-hour $LC_{10,\ 50,\ 90}$ values were 89, 124, and 173 ppm, respectively (Dow Chemical, 1976). Goldfish tolerated a continuous 30-day exposure to acrylamide in water at 50 ppm without signs of intoxication. Exposure to 100 ppm, however, was lethal in five to seven days. No signs of neuropathy were noted in sublethal exposures (Edwards, 1975b). Similarly, blackhead minnows survive for over two weeks in acrylamide concentrations of 60 ppm but show marked mortality at concentrations of 1000 ppm (Renn, 1956).

Tadpoles can absorb acrylamide from aqueous solutions with labeled material being bound to the brain, nerves, and other organs (Tarusov et al., 1966a and b).

4. Effects on Invertebrates

No studies encountered.

5. Effects on Plants

Although no studies have been encountered on the toxicity of acrylamide to plants, Ismailova (1966) indicates that acrylamide at concentrations of 0.1, 0.5, and 1.0% inhibits the development of Pseudomonas tumefaciens-induced tumors in plants. Acrylamide has similar activity on some mammalian tumors (see Section III-B-2-h, p. 119).

6. Effect on Microorganisms

No detailed study has been reported concerning the effect of acrylamide and its derivatives on microorganisms. Cherry et al. (1956), by microscopic examination of river water which had been treated with 10 ppm acrylamide, found that the biota which developed in the water was mixed and healthy. When acrylamide was added with acrylonitrile, they noted a selective enrichment of a type of "spined" cell. It appears likely that these cells increased in number by virtue of their ability to tolerate and/or degrade the test compounds.

7. In Vitro and Biochemical Studies

a. Effects on Isolated Organs

Incubation of rat brain stem cortex slices with 10 mM acrylamide has no effect on oxygen consumption or on the final concentrations of pyruvate and lactate (Hashimoto and Aldridge, 1970).

b. Effect on Cell Cultures (Non-Microbial)

Spencer et al. (1976) utilized organotypic spinal cord-peripheral nerve-spinal ganglion-striated muscle combination tissue cultures to study the neurotoxic effects of acrylamide in vitro. Acute fiber breakdown was noted after one week of exposure to 100 μg/ml of nutrient fluid and no effect was noted after six weeks of exposure to 1 μg/ml. Twenty-five μg/ml produced neurotoxic effects in sensory axons after two to three weeks and distal axonal degeneration by twelve weeks. Scattered demyelination was also a pronounced feature.

Kuperman (1957) has shown that acrylamide, but not acrylamide analogs, will harden whole human blood at acrylamide concentrations of 300-600 g/ℓ. Kojima and coworkers (1971) have shown that acrylamide and a number of other vinyl monomers will undergo graft copolymerization with whole blood.

c. Effect on Isolated Organelles and Cell Homogenates

Hashimoto and Aldridge (1970) indicate that acrylamide at 10 mM concentration does not inhibit oxidative phosphorylation in rat liver mitochondria.

d. Effects on Purified Enzymes and Isolated Enzyme Systems

No studies encountered.

e. Effects on Nucleic Acids and Proteins

As indicated previously (see Section III-B-2-b, p. 75), acrylamide and N-methylolacrylamide undergo glutathione conjugation and lower non-protein sulfhydryls in rat brain, spinal cord, and liver. Hashimoto and Aldridge (1970) have determined the reactivity of these two acrylamides and a number of related compounds with glutathione in vitro. The results are summarized in Table 36. The reactivity of these compounds with glutathione does not correlate to their neurotoxicity. Acrylamide and N-methylolacrylamide are equally reactive with glutathione. This has also been noted by Edwards (1975a). However, acrylamide is at least three times more potent a neurotoxin than N-methylolacrylamide. Similarly, neither acrylonitrile (more reactive) nor sodium acrylate (less reactive) are neurotoxic.

Table 36. **Reactivity of Acrylamide and Its Analogs with Glutathione at pH 7.3 and 37°C *In Vitro* (Hashimoto and Aldridge, 1970)**

Compounds	k $l.mole^{-1}min^{-1}$
Acrylonitrile	2.42
Acrylamide	0.91
N-Methylolacrylamide	0.91
N,N'-Methylenebisacrylamide	0.54
Ethyl Crotonate	0.24
N-Methylacrylamide	0.058
N,N-Diethylacrylamide	0.058
Sodium Acrylate	0.035
Methacrylamide	0.014

Similar to Kuperman's (1957) observation on solidification of whole blood by acrylamide (p. 124), Druckrey and coworkers (1953) found that acrylamide causes a number of different protein solutions to solidify. This may have been due to polymerization of the acrylamide. The order of reactivity for different proteins was: fibrinogen > gamma globulin >> human serum > serum albumin. Cavins and Friedman (1967a) have demonstrated that acrylamide alkylates with the sulfhydryl groups of bovine serum albumin and wheat gluten. However, the reactivity of acrylamide is less than that of either acrylate or acrylonitrile (see also Cavins and Friedman, 1976b). The order of reactivity is different than noted by Hashimoto and Aldridge (1970) for in vitro conjugation with glutathione. In addition, Hashimoto and Aldridge (1970) have found that four moles of acrylamide bind to one mole of hemoglobin, implying that binding occurs at the four active sulfhydryl groups.

No in vitro studies have been conducted on the alkylation of acrylamide to nucleic acids. As indicated previously (see Section III-B-2-a, p. 73), small amounts of label from [1-^{14}C]acrylamide appear in both the RNA and DNA fractions of rat brain and liver one day after dosing.

IV. Regulations and Standards

A. Current Regulation

1. Food, Drug, and Pesticide Authorities

The Food and Drug Administration (FDA) has approved the use of acrylamide and certain acrylamide derivatives in polymeric formulations intended for contact with food. Sodium polyacrylate-acrylamide resin may be used to control organic and mineral scale in beet and cane sugar juice or liquor, so long as residual acrylamide monomer levels do not exceed 0.05% (FDA, 1972c) Acrylamide along with styrene may be used in preparations of N-[(dimethylamino)methyl]acrylamide as dry strength agents for paper or paperboard intended for food contact. This formulation may not exceed 1% by weight of the finished paper product and acrylamide monomer may not exceed 0.2% by weight of the formulation (FDA, 1974a). Modified polyacrylamide - residual monomer content unspecified - is permitted in paper or paperboard intended for contact with dry food when used as dry strength or pigment retention aids (FDA, 1972a). Acrylamide and ethylene may be copolymerized with vinyl chloride for use in coatings on food contact surfaces. No more than 3.5% by weight of total polymer units may be derived from acrylamide (FDA, 1974b).

Homopolymers and copolymers of N,N-methylenebisacrylamide or N-methylolacrylamide may be used in food packaging adhesives. Residual monomer levels are not specified (FDA, 1965). A reaction product of N-(1,1-dimethyl-3-oxybutyl)acrylamide and formaldehyde may be used in levels up to 1% as components of polyvinyl acetate latex coatings for paper and paperboard intended for use in contact with food (FDA, 1972b).

The USPHS has approved polyacrylamides for potable water treatment with the provision that the dose of polymer does not exceed 1 ppm and that the polymer contains not more than 0.05% monomer (MacWilliams, 1976).

2. OSHA

The Occupational Safety and Health Administration (OSHA, 1975) is currently developing a criteria document on acrylamide. Present standards are identical to the TLV, allowing 0.3 mg/m^3 in workroom air (OSHA, 1974).

3. Other Federal, State, and County Regulations

None encountered.

4. Foreign Countries

In England, levels of acrylamide in water clarified using polyacrylamide have been established. Polyacrylamide may contain up to 0.05% acrylamide monomer. The maximum concentration of acrylamide monomer in clarified water may not exeed 0.5 µg/liter, and the maximum average concentration may not exceed 0.25 µg/liter (Housing and Local Government Ministry, 1969).

In Russia, the suggested maximum permissible concentration of methacrylamide and N-methylolmethacrylamide in potable water is 0.1 mg/liter (Strizhak, 1967).

B. Consensus and Similar Standards

1. TLV

The American Conference of Governmental Industrial Hygienists (ACGIH, 1974) have recommended 0.3 mg/m^3 (0.1 ppm) as the TLV for acrylamide in workroom air. This standard is based on the daily exposure limit recommended by McCollister and coworkers (1964) - see Section 3 below.

2. Public Exposure Limits

None encountered.

3. Other

McCollister and coworkers (1964) have recommended that daily levels of acrylamide exposure to humans should not exceed 0.05 mg/kg in the workplace and should not exceed 0.0005 mg/kg to the general population. This recommendation is based on subacute and chronic testing of various laboratory mammals (see Section III-B-2-c, d, p. 78 , 85).

Spencer and Schaumburg (1975) have recommended periodic examinations of workers exposed to acrylamide and are currently developing an assay for the early detection of acrylamide intoxication based on polymer sensitivity.

V. Summary and Conclusions

There are nine acrylamide compounds that are produced in commercial quantities. However, acrylamide itself is by far the most important in terms of production volume. In 1973, the annual production of acrylamide was estimated at 40 million pounds. It is believed that the derivatives are all produced in significantly smaller quantities than acrylamide.

The major use of acrylamide and its derivatives is in the production of polymers and copolymers for a variety of applications. Linear polyacrylamides are used because of their solubility in water, polar functional groups, low toxicity, and competitive cost. The largest market for polyacrylamides (~ 40%) is as a flocculant in sewage and waste water treatment. They are also approved for treatment of potable water, but the residual monomer in the polymer must be below 0.05%. Another major application (~ 20%) is in the pulp and paper industry as a strengthener and to aid in preventing fibers from being washed away. Minor applications for polyacrylamides include drilling fluid additive, secondary oil recovery agent (a fast growing application), chemical grouts and soil stabilizers (one of the few applications in which acrylamide monomer is polymerized *in situ*), adhesives, coal flotation and coal dust loss prevention, textile treatments, printing paste, photographic applications, etc.

Losses to the environment from production, transport, and storage of acrylamide are considered to be minor. The major source of acrylamide monomer loss to the environment appears to be from the use of polyacrylamide products which contain residual acrylamide monomer. In addition to losses of acrylamide from polyacrylamide, another source of contamination is the direct use of acrylamide monomer to soil as chemical grouts and soil stabilizers for dams, foundations, tunnels, etc. Although no United States monitoring information is available, this loss of residual monomer is supported by British monitoring data where concentrations as high as 42 μg/ℓ (ppb) were detected in effluents from coal mines and preparation plants, paper mills, and clay pits. In the case of the clay pit, the concentration of acrylamide in the receiving stream was 1.2 μg/ℓ, and further downstream at a waterworks intake the level dropped to 0.3 μg/ℓ, which is still above the average permissible level for drinking water (0.25 μg/ℓ). The concentration of acrylamide in conditioned sewage sludge at two sewage conditioning plants which used polyacrylamide was well below 0.1 μg/ℓ. The residual monomer in polyacrylamide used for potable water treatment is regulated, but any improper uses of polyacrylamide with uncontrolled monomer residual in potable water treatment could result in substantial exposure to humans.

A number of studies indicate that acrylamide will biodegrade in the environment as well as under biological sewage treatment conditions. Acclimation of the microorganisms appears to be necessary. The importance of non-biological alterations of acrylamide in the environment is unknown.

The high water solubility and low vapor pressure of acrylamide suggest that acrylamide released to the environment will reside in aquatic systems. The calculated evaporation half-life from water is ~ 400 years. The high water solubility also suggests that bioconcentration should not be an important process with acrylamide.

Based on these patterns of use, release, and environmental fate, as well as the known biological effects of acrylamide and acrylamide analogs, three areas of potential environmental concern are apparent: neurotoxicity, carcinogenicity, and toxicity to aquatic organisms.

Of the commercially important acrylamide compounds, acrylamide itself has the greatest neurotoxic potency. However, the dose-response patterns for neurotoxicity have been relatively well-defined in a number of mammals, and these patterns indicate that prolonged exposure to probable environmental concentrations would not produce apparent neurotoxic effects. On acute exposures, acrylamide primarily affects the central nervous system (CNS) and characteristically causes ataxia, weakness, tremors, and convulsions. Single oral or intraperitoneal doses of 100-200 mg/kg cause severe CNS effects and are often fatal to laboratory mammals 1-3 days after dosing. The acute effects of substituted acrylamides have not been studied in great detail. Acute oral LD_{50} values for these compounds range from about 300 mg/kg to over 1000 mg/kg.

Repeated exposure to acrylamide and some acrylamide derivatives causes a clinical peripheral neuropathy which is associated pathologically with a central and peripheral distal axonopathy. Characteristic symptoms of chronic intoxication include ataxia, bilateral weakness of the hind limbs which may progress to limb paralysis, and loss of proprioception. In addition, sensory impairment, bladder distention, weight loss, vocal changes, and various other secondary effects have been noted in some experimental mammals. Clinical signs of neurological impairment are associated with consistent histological and physiological changes, including axonal degeneration with demyelination and decreased nerve conduction velocity. Even in cases of severe intoxication, clinical, histological, and physiological signs of damage seem to be reversible.

The dose necessary to cause early signs of neurological damage over exposure periods of up to about six months seems to be dependent primarily on the cumulative dose rather than the dose schedule or route. For acrylamide, the total effective cumulative dose is in the range of 300-600 mg/kg. As in acute exposure, the acrylamide analogs are markedly less potent. Acrylamide-like neuropathy has been demonstrated by only three of these analogs: N-methylolacrylamide, N-methylacrylamide, and N,N-diethylacrylamide. While potency estimates vary somewhat among the available studies, the two monosubstituted acrylamides are probably no more than 30% as potent as acrylamide, while N,N-diethylacrylamide is only about 5% as potent. Two additional acrylamides, N,N-dimethylacrylamide and N-isopropylacrylamide, also have neurotoxic effects, but these effects have not been described in detail.

The chronic neurotoxicity of acrylamide and some acrylamide derivatives is without doubt a cause for concern in occupational exposures. Cases of acrylamide-induced neuropathy in workers have been well-documented and the signs of neuropathy in humans generally resemble those seen in laboratory mammals. However, the relationship between the extent of exposure and the specific neurological signs that develop is unclear. Mammalian studies suggest that prolonged exposures to low daily doses of acrylamide do not produce signs of neurotoxicity even when cumulative doses exceed the neurotoxic threshold of shorter exposure periods. Given that the peripheral neuropathic effects of acrylamide are apparently reversible, the daily exposure limit of 0.05 mg/kg/day in the workplace and 0.0005 mg/kg/day in the general population recommended by McCollister and coworkers (1964) and adopted by AGCIH (1974) and OSHA (1974) does not seem unreasonable. With the extremely low levels of acrylamide that can be expected in the environment, widespread neurotoxic effects due to acrylamide contamination seem unlikely. However, the possibility of human neuropathy resulting from local incidents of acrylamide contamination cannot be disregarded.

The carcinogenic potential of the acrylamides does seem to be a legitimate area of environmental concern. The carcinogenicity of the acrylamides has not been studied directly. However, the appearance of ^{14}C-labeled RNA and DNA after exposure to [1-^{14}C]acrylamide and the ability of acrylamide to alkylate with protein would seem to indicate that carcinogenicity screening studies should be performed on acrylamide and some of its commercially important analogs before a definitive assessment of environmental hazard can be made.

The information on the toxicity of acrylamide to life forms other than mammals is not extensive. While the available information does not indicate a remarkably high toxicity to hens, frogs, or fish, additional information on aquatic biota might be desirable in order to assess potential local contamination.

Thus, the potential of a widespread environmental hazard associated with the commercial use of acrylamide or polyacrylamide products does not seem very high. Most of the acrylamide is polymerized to a stable resin. Dilute concentrations of residual acrylamide monomer are leached out of the polymer in many of the aqueous applications of polyacrylamide. However, the concentrations are low and acrylamide is biodegradable; it probably does not bioconcentrate; and its neurotoxic effects are largely reversible and appear to have a threshold concentration above likely environmental concentrations. Nevertheless, there may be some instances where the concentration of acrylamide emitted from polyacrylamide use could result in excessive concentrations of acrylamide in water, with possible adverse effects on aquatic ecosystems and/or human health. It would therefore seem appropriate to examine the various applications of polyacrylamide (including direct application of acrylamide monomer to soil) more intensively to determine which of these applications could result in such incidents, the precipating factors, and viable procedures to preclude such occurrences. Some selective monitoring should be part of any assessment.

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